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ADVANCES IN PRACTICAL PREVENTION OF GYNECOLOGIC CANCER*

ROBERT J. CROSSEN, M.D., ST. LOUIS, MO.

THE treatment of cancer is being constantly improved, but the prevention of cancer constitutes the greater lifesaving measure and a most stimulating pioneer field. Cancer prevention is no longer in the theoretical, hazy, wishful-thinking stage. It is here in practical application in day-to-day work. This applies to cancer of the ovary and of the uterus and of the external genitals. As the gynecologist goes about his work he is able to take measures to prevent cancer, instead of waiting till its development jeopardizes the patient's life in spite of the use of the most radical treatment. The development of this preventive work has not been an easy task, but it is here now in effective application. Furthermore, this is a method of lifesaving in which the general practitioner can participate in his daily work, and in which he must take a prominent part, and attain corresponding credit for effective service to his patients.

The prevention of carcinoma in the structures mentioned is made possible by the recognition of two common conditions as predisposing factors, namely, chronic irritation and involution changes. There are many things about the origin of cancer which are still unknown, in spite of the investigations going on in institutions all over the world. But the predisposing influence of chronic irritation and of the involution process are well-established facts which have been known a long time. The advances in cancer prevention which I wish to emphasize have come through the application of this long-known knowledge to the actual handling of patients. The presentation may be divided into two parts—the removal of chronic, irritation and the removal of involuting organs.

Removal of Chronic Irritation

In recent years much excellent work has been done by physicians and organizations in promoting one phase of the cancer-prevention problem. In

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addition to the educational publicity given the signs of uterine cancer, which resulted in patients with cancer coming in earlier stages, there has been increasing recognition of the fact that chronic irritation is a predisposing factor and that it should be removed, and that examinations are advisable to detect it while a simple and easily-cured condition. These efforts have dealt principally with carcinoma of the cervix uteri, and in that particular have rendered splendid service, and the removal of chronic cervicitis before cancer develops is gradually spreading throughout the profession in the daily care of patients.

Incidentally, in removing chronic cervicitis, it is important to remove the affected tissue in a way which permits of microscopic check of all of it. The preferable plan is conization. The special electrode, extending the Hyams conization to removal of extensive cervicitis, was devised and reported in 1935.[1-2] Where conization facilities are not available, conical excision with a knife removes the tissue in a condition permitting thorough microscopic check. But to destroy the affected tissue by cauterization or coagulation, which precludes complete microscopic check, is to invite the risk of overlooking an early cancer. What appears to be simple cervicitis may harbor an area of beginning carcinoma with no indication on the surface of what is going on underneath. A specimen excised before cauterization or coagulation is not sufficient, for the microscopic cancer may be in another part of the affected area.

That removal of cervicitis does really prevent cancer is shown by available statistics. Craig[3] found that in 2,895 cases of cervicitis treated adequately and then followed for a period of ten years or more, not one patient developed cervix cancer. Hence, according to the usual estimates (cancer in 4 per cent of gynecological patients, with 89 per cent in cervix), cancer was prevented in more than one hundred of these patients. Karnaky,[4] reporting statistics from the Jefferson Davis Hospital, found that in the preceding ten-year period there were over 5,000 conizations. In the same period there were 709 cervical cancers. Not one cancer developed in a conized cervix.

In doing hysterectomies, the cervix should be removed. If there is some contraindication to complete hysterectomy, the cervix should be coned.

In connection with chronic irritation, it is important to mention another area in which the persistence of certain forms of irritation is closely related to subsequent cancer. That area is the external genitals, and one such form of chronic irritation is leucoplakic vulvitis. The skin becomes atrophic and white, and there is persistent itching and irritation from scratching, which distinguishes it from simple symptomless leucoderma. Taussig's investigations and accurate recording and analysis of extensive clinical experience with leucoplakic vulvitis established it as one of the important diseases of the external genitals. It causes marked distress at various stages of progress; effective treatment usually requires an extensive and particular plastic operation, and, if allowed to persist, it is very likely to eventuate in cancer.

In Taussig's[5] series of 155 cases of vulvar cancer, he found that in almost half of them the cancer was preceded by leucoplakic vulvitis. In regard to prevention of cancer, he states: "I am convinced that we have been very

remiss in our preventive measures in the past. The incidence of vulvar cancer might very possibly be cut in half if we would adopt complete vulvectomy in cases of well-developed leucoplakic vulvitis, and give critical attention to vulvar warts and urethral caruncles and other chronic irritative lesions. Particularly, in leucoplakic vulvitis would I stress the advantages of surgery over nerve resection or treatment with ovarian hormones. The latter undeniably often decreases the pruritus, but the question whether the use of such carcinogenic substances may not at least predispose to the development of a cancer might very well be raised."

Removal of Involuting Organs

Another fact which has long been known is that the involution process favors cancer development. That is why carcinoma occurs so much more frequently in persons past middle life. It is only recently, however, that this well-established fact is being practically applied to cancer prevention.

As there is no way to stop the aging process, and as aging persons wish to live out their span of life, there did not seem much chance to use the knowledge stated in cancer prevention. However, there are two organs which go through involution shortly after middle life, namely, the uterus and the ovary. They are temporary organs, their functioning being limited to the childbearing period. After the menopause they are no longer functioning organs, but involuting structures on their way out of the active economy. They touch no vital interest of the individual—their special task of childbearing with its associated hormone production has been performed and finished. They are not only functionless, but they carry the special menace of involuting structures, which is a predisposition to cancer development.

Involuting Ovaries.—The most serious menace comes from cancer of the involuting ovary. Though less frequent than cancer of the uterine endometrium, the usual symptomless progress to incurability of ovarian cancer causes it to be fatal in a much larger proportion of the cases.

Primary ovarian carcinoma is the most insidious of the pelvic malignancies, and the one most frequently overlooked until it has reached a hopeless stage. It causes so little disturbance that most patients do not realize there is anything wrong until the malignant infiltration has advanced beyond cure. Attention was called to this striking phenomenon by H. S. Crossen[6] and the menace is so serious and the recognition of the condition so important to all physicians that considerable space is taken here to bring out the details by the following quotations from the article:

"By 'silent' I mean without symptoms—without any indication to the patient that a serious process is present. Patient after patient is seen with an extensive growth of long duration but with only a short period of local symptoms. The first visit to the physician shows a large growth or ascitic fluid from peritoneal carcinosis. The advancing carcinoma causes only such minor disturbances that the patient hardly notices them. Thinking back, when questioned, she recalls that the abdomen has been a little larger for a year or so or that there was bloating or some frequency of urination, but only in the last few

weeks was there enough disturbance to make her feel that perhaps an examination was advisable. Some examples from my experience will serve to illustrate the point.

Report of Cases

"Mrs. S., aged 56, had a gradual loss of weight for two years but no local symptoms till a few months before consulting a physician, and even then there was only indefinite discomfort in the abdomen and back. Abdominal examination showed a mass in the left side projecting up from the pelvis, and the patient was sent for operation. The operation revealed an extensive carcinoma of the ovary, which had already invaded irremovable structures. The main tumor was removed and roentgen therapy was given for the extensions. Repeated roentgen treatments prolonged life in fair comfort for a year.

"Mrs. H., aged 52, had come under my care at the age of 47 for treatment of a retrodisplaced myomatous uterus with some prolapse and menstrual irregularity and hot flushes. At that time she was put on conservative treatment and directed to return in two months. She did not return for five years because as she stated, 'There was no special disturbance, and I felt well right along until some months ago.' The principal symptom when the patient came at the age of 52 was enlargement of the abdomen. She thought this had come on gradually, but in the last two weeks it had become well defined and was accompanied with discomfort and an occasional pain. Examination showed pronounced ascites with some masses in the pelvis. Operation revealed general abdominal carcinosis of ovarian origin. No structure could be removed except a specimen for microscopic diagnosis.

"Mrs. P., aged 47, had noticed enlargement of the abdomen for two months, with a feeling of pressure, soreness and frequency of urination for six weeks. Examination showed a pelvic mass extending halfway to the umbilicus. At operation I found a carcinoma of the right ovary with extension to the uterus and other ovary and tube and also to the adherent appendix and abdominal wall. The main mass was removed along with the uterus, the other ovary and tube, the appendix and a specimen from the involved abdominal wall. In each of the structures mentioned, including the abdominal wall specimen, the extension of carcinoma was confirmed by microscopic examination. Postoperative roentgen therapy was employed, with unexpectedly good results. The operation was in 1933, and the patient is still well and strong and without evidence of recurrence. The patient was a physician's wife. Her sister had died of ovarian carcinoma and her mother of cancer of the stomach. In spite of these facts favoring close observation, the growth of the ovarian cancer was so 'silent' that it had extended into surrounding structures before there was any intimation of its presence.

"Miss R., aged 48 years, was a patient for whom, at the age of 43, I had performed a hysterectomy for myoma with right salpingo-oöphorectomy and appendectomy, and recovery was without special incident. Five years later she was sent by her physician for treatment of a pelvic tumor extending almost to the umbilicus. She had noticed some pressure in the abdomen for about a year but gave little thought to it. An increase in the pressure discomfort finally caused her to go to her physician, who found the tumor. Operation showed extensive abdominal carcinosis originating in the left ovary. No structure could be removed. Repeated roentgen treatments kept the patient in fair comfort for nearly a year.

"The lesson of this case is that I should not have left an ovary at age 43. I thought then that it was advisable, but I know better now.

"Mrs. G., aged 55 years, went to her physician because she had noticed discomfort in the left side of the lower part of the abdomen off and on for a month or two. Examination showed a tumor the size of a fist filling the left side and central portion of the pelvis. Operation revealed a carcinoma of the left ovary. It had already spread to adjacent organs and into irremovable structures. The main mass was removed, and with roentgen therapy the patient lived for a year and eight months."

And so on, with depressing regularity, down the series of twelve cases the victim notices some bloating and enlargement of the abdomen, comes for examination which shows ascitic fluid with a pelvic mass, and operation reveals an extensive irremovable ovarian carcinoma. Continuing to quote:

"These 12 cases show the symptomless progress to extensive involvement which represents the natural history of ovarian carcinoma. Some patients are fortunate enough to have some coincident disease which takes them to a physician, who, in the course of routine pelvic examination, discovers the silent growth before it has progressed beyond removal. Occasionally some early complication of the growth causes pain which leads to examination and discovery of the cancer in a curable stage. The favorable cases of ovarian cancer are discovered thus through routine examination or accidental complication. These fortunate exceptions must not be allowed to divert attention from the symptomless onset and symptomless progress of uncomplicated ovarian cancer. It is ordinarily a slow-growing infiltration which penetrates into irremovable structures before the appearance of warning symptoms.

"The aggregate of deaths from this cause is large, much larger than is generally appreciated. To the known cases must be added the unrecognized ones, with death certificate designations of 'ascites' and 'abdominal cancer.' A large proportion of the cases of general abdominal carcinosis originate in an ovary.

"The silent character of the onset and progress of ovarian cancer seals the doom of these individuals, unless measures which are really effective against the serious difficulties of the situation are put into practice. The following three steps are advisable and urgent in reducing deaths from this insidious disease:

"1. Removal of the involuting ovaries whenever the abdomen is opened under circumstances which permit of such removal.

"2. Insistence on regular periodic pelvic examinations. These periodic examinations for silent ovarian carcinoma should be made every six months, instead of the once yearly which was formerly supposed to provide adequate safety. Also, one must give the time and thought necessary to make this advice of real benefit to each patient, instead of simply throwing out some general remark to act as a salve to conscience should the patient return later with incurable cancer.

"3. Utilization of every opportunity afforded by anesthesia for a minor vaginal operation, to make deep accurate palpation of the ovarian areas, the findings to be recorded in the operative note for future reference and comparison."

Involuting Uterus.—Since our study of the cancer menace in involuting ovaries and the advisability of their removal in suitable cases whenever the abdomen is opened in the age of involution, we have given much thought to the problem of choice between radical and conservative treatment of nonmalignant uterine lesions which are giving the patient so much trouble that serious treatment is required. This problem is encountered when handling patients with uterine myoma causing troublesome symptoms which persist in spite of palliative measures. Of course, some myomas cause no symptoms and require no treatment, while in other cases the troublesome symptoms may be sufficiently relieved by minor measures. But persisting serious symptoms confront us with the problem of choosing between operative removal of the fibroid and stopping its activity by radiation.

Radiation treatment is, of course, contraindicated in the childbearing period, and also in those cases in which the myoma is causing trouble that would not be relieved simply by cessation of ordinary myoma activity. On the other hand, there are many myoma patients in the age of involution, whose bleeding and other troublesome symptoms can be entirely relieved simply by curettage to exclude to malignancy, conization when cervicitis is present, and radium treatment to stop myoma activity. This takes care of the immediate disturbance without the serious risk of hysterectomy, but it does not remove the involuting uterus and ovaries with their risk of future malignancy.

How do these two risks compare? What weight should be given to each, in advising the patient? In order to answer these important questions, we must know (a) the risk of hysterectomy with double oophorectomy, and (b) the risk of future malignancy in these involuting organs, without radiation and with radiation. From general operative statistics we know the average mortality risk in removal of the uterus and ovaries for myoma or other nonmalignant condition. With an experienced operator it may be reckoned at 1 to 2 per cent, depending on the condition of the patient. In order to obtain definite information as to the future-malignancy risk in myoma patients treated by radiation, as well as to obtain definite information on many other items, we made an analysis of our series of 549 myoma patients selected for myoma radiation, and recently reported the results.[7] The plan of procedure included curettage to exclude malignancy, conization when there was cervicitis, and an intrauterine radium treatment. Incidentally, it may be mentioned that the primary curettage revealed a complicating endometrial carcinoma in 23 of these 549 patients who appeared to have only a simple fibroid.

In regard to malignancy development in patients with myoma, in our series of 2,662 myoma patients 526 were treated by radiation, and the malignancy developments in the two groups are shown in the following table.

Cancer of Endometrium	In 2136 nonradiated myoma cases.	37 (1.7%)
	In 536 radiated myoma cases.	4 (0.7%)
Cancer of Ovary	In 2136 nonradiated myoma cases.	13 (0.68%)
	In 536 radiated myoma cases.	1 (0.19%)

Each type of malignancy was more than twice as frequent in the nonradiated cases as in the radiated.

Here we have dependable data as to the future malignancy risks in myoma patients with involuting organs. Without radium treatment, the malignancy risk for uterus and ovaries is 2.38 per cent. With radium treatment, the risk is 0.89 per cent. Thus the radiation procedure which we employed not only took care of the immediate trouble in most cases, but also cut to one-third the risk of future malignancy. However, it did not eliminate that risk—as operative removal would have done, but at a decided immediate mortality risk.

Decision as to what is safest and best for each patient requires a careful assessment for that individual of the three important factors—the chance of satisfactory relief by the radiation procedure, the risk of later malignant devel-

opment, and the risk of a major operation. The wish of the patient is another factor which has some bearing on the decision. Some patients would decidedly prefer the myoma-radiation program, with its minor immediate risk and subsequent oversight, rather than the major operation with its greater immediate risk and greater future security.

Our conclusions as to the place of radium treatment in the handling of climacteric patients with troublesome myoma, keeping in mind the cancer potential in the involuting ovaries and uterus, are as follows:

1. It is effective in stopping myoma activity and associated troublesome symptoms in 90 per cent of properly selected cases.

2. It reduces to one-third the risk of future malignancy. But it still leaves a risk of 0.89 per cent, which definite risk must be given due weight in deciding between radium treatment and operative removal, in the individual patient with her special local and general conditions.

3. When the patient is a good operative risk and has first-class operative facilities available, removal of the complete uterus and the involuting ovaries would seem the safer plan.

4. For the handicapped patient with high operative risk, the myoma-radiation plan here described is a lifesaving measure and strongly indicated, where the serious symptoms are of a type to be relieved by it.

A word about delayed menopause as an indicator of increased susceptibility to malignancy. Delayed menopause (prolongation of periodic flows up to ages 48, 50, and 52 years, and older) does not signify "renewal of youth," as some women suppose. It signifies persisting ovarian stimulation keeping up uterine congestion and erratic activity in involuting organs, which means an increased cancer potential in the endometrium of that individual.

In 1935, Dr. Hobbs and I analyzed a series of fundal carcinoma cases to determine whether delayed menopause, with its prolonged estrogenic activity, was more common in endometrial, carcinoma cases than it was in normal cases. We found that in 60 per cent of the carcinoma cases the patients had menstruated to the age of 50 years in contrast with only 15 per cent in the normal cases. In a recent article, Randall calls attention to the frequent association of delayed menopause and corpus cancer. He also found that delayed menopause was four times more frequent in malignant cases than in the nonmalignant ones.

In summarizing, then, we can say that, though the specific cause of endometrial carcinoma is not yet known, circumstantial evidence points to the prolonged action of endogenous estrogen beyond the normal menopause age as an important factor. Hence the importance of eliminating this abnormal influence, for the longer it continues the greater the likelihood of carcinomatous development in the involuting endometrium. This sinister influence can be easily eliminated by radium treatment, which stops the erratic ovarian activity. Curettage along with the radium treatment determined whether or not malignant change has already begun.

It may be well to add here a word of warning concerning the use of estrogenic hormones in the menopause, and particularly in patients with delayed menopause. Bleeding beyond the usual age calls, not for estrogenic medication but for investigation to determine if endometrial carcinoma has already begun. In view of evidence presented, it would seem unwise to use large doses or prolonged dosage of estrogenic substances in patients in the menopause age. If there are troublesome symptoms, Engle has shown that most of the menopausal symptoms can be controlled by small doses of thyroid plus phenobarbital. If in spite of this, hot flushes continue to a troublesome extent, stilbestrol may be added, but in minimum doses required to give relief.

Résumé

1. Cancer prevention involves the removal of chronic irritation, by conization for cervicitis and by vulvectomy for leucoplakic vulvitis, and the removal of involution ovaries and uterus under suitable circumstances.

2. Periodic examinations are necessary to discover chronic irritation before malignant development starts and to discover cancer in involuting ovaries or uterus or breasts while it is still in a curable stage.

Yearly checkups were formerly considered sufficient, but owing to the difficulties of detecting early ovarian cancer that interval is too long to guard the patient against advanced malignancy. That fact was learned by bitter experience. A patient whose adnexal areas were apparently clear on examination returned seven months later with an irremovable ovarian cancer. Careful checkups at six-month intervals for the two decades, aged 40 to 60 years, constitute the minimum requirement for reasonable safety from incurable malignancy.

3. In addition to the usual deep pelvic palpation and the speculum examination and the check of the breasts for beginning infiltration, the checkup should include percussion of the flanks for possible ascitic fluid. A small amount of free fluid in the peritoneal cavity is often the first demonstrable sign of the chronic peritoneal irritation associated with ovarian carcinomatous infiltration.

4. Owing to the cancer-potential of the involuting ovaries and the "silent" advance to incurability of most ovarian cancers, it is advisable to remove the involuting ovaries whenever the abdomen is opened in the climacteric age (43 years and later), except where there is some definite contraindication to this additional work.

5. The cancer-potential of the involuting endometrium should be taken into consideration when handling nonmalignant uterine conditions requiring serious treatment. For example, a myoma causing persistent serious symptoms in spite of palliative measures confronts us with the alternative of stopping the myoma activity by radium treatment (with curettage to exclude malignancy and conization if cervicitis is present) or removing the growth by the major operation of hysterectomy.

This calls for careful consideration of three factors, namely, (a) the chance in that particular case of securing relief by the radiation program, (b) the future risk of malignant development in uterus or ovaries, and (c) the immediate risk of hysterectomy and double oophorectomy. In our report of five hundred myoma-radiation cases, previously referred to, may be found tabulated the cases given permanent relief and those not relieved. Also, we found that though the risk of future malignant development was cut to one-third by radium treatment, there still remained a malignancy risk of 0.89 per cent. The mortality risk of hysterectomy and double oophorectomy may be reckoned at 1 to 2 per cent, depending on the condition of the patient and the skill of the operator. Giving proper weight to these various factors in your study of the individual case will insure the safest and best treatment to your patient.

In general, for the good operative risk, the seriously troublesome myoma occurring in the age of involution is preferably handled by complete hysterectomy and double oophorectomy. On the other hand, for the seriously handicapped patient the radium plan in a suitable case is a lifesaving measure, in that it stops the serious myoma activity without the great risk of a major operation.

6. Leucoplakic vulvitis eventuates in cancer in a considerable proportion of the cases. In Taussig's series of 155 vulvar cancers, nearly half were preceded by leucoplakic vulvitis. Hence, the importance of prompt vulvectomy for this condition, unless there is a good response to vitamin A therapy as suggested by Hyams and Bloom.[8]

7. Delayed menopause indicates erratic endometrial and ovarian activity which increases the susceptibility to malignant development. It should be stopped by radium treatment, with associated curettage to exclude endometrial malignancy, conization if cervicitis is present, and accurate palpation of the ovarian areas under the anesthesia, with recording of findings for future reference and comparison.

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A STUDY OF THE CAUSES OF FETAL AND NEONATAL MORTALITY ON THE OBSTETRIC SERVICE OF BELLEVUE HOSPITAL

JOHN S. LABATE, B.S., M.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Service [Third Division], The Laboratories of Pathology, Bellevue Hospital and The Department of Obstetrics and Gynecology, New York University)

FETAL and neonatal mortality rates are directly proportionate to progress made in maternal and infant care. We cannot remain satisfied with our maternal and infant care programs until we have made definite strides toward an appreciable reduction in these mortalities. While a definite reduction in the maternal mortality rate of the U. S. has been recorded in the past decade, the reduction in the fetal and neonatal mortality has not been proportionate.

In 1945, there occurred 105,000 fetal and neonatal deaths, the latter category accounting for 10.4 per cent of the total deaths in the U. S. in the first month of life[9] from all causes. The high mortality rate compares closely to the rates accorded to the major causes of death among our general population. It is as important to reduce the number of deaths among newborn infants as it is to reduce the death rate from cancer, heart disease, or tuberculosis.

In New York City, the stillbirth and neonatal (first month of life) mortality rate for 1944 was 31.2 per 1,000 live births, as compared with 57.2 per 1,000 live births in 1930. The rate of reduction of fetal and neonatal mortality in the United States has been progressive, but slow. The infant mortality rate for 1945 in the United States according to recent estimates of the Bureau of Census is the lowest on record, 38.1 per 1,000 live births. The corresponding rate for 1944 was 39.2. Despite this decrease, concern has been voiced over the relatively high fetal and neonatal death rates.[5, 10, 11]

In order to effect an adequate reduction in the fetal and neonatal mortality rate, it is important to obtain accurate information concerning the causes of death in stillbirths, and in newborn infants. Efforts then can be directed toward the control of the major factors influencing these results. This object we can obtain best through careful autopsy examinations correlated with the clinical facts related to this fatality. The causes of death as ascertained from death certificates are too vague and misleading, since most are not supported by postmortem examination. Such a study of fetal and neonatal mortality can best be carried out on a large obstetric service. This presentation is an attempt to analyze the causes of such deaths on the obstetric service of Bellevue Hospital.

During the ten years beginning on July 1, 1933, and ending May 31, 1943, 16,669 deliveries took place in Bellevue Hospital. During this period, there were 1,114 fetal and neonatal deaths. The uncorrected mortality rate was 6.6 per cent. After excluding 312 nonviable infants, the corrected fetal death rate was 4.8 per cent. The death rate among term infants during this period was

1.97 per cent, while the mortality rate among viable premature infants was 35.2 per cent (Tables I and II). Eight hundred sixty-eight or 77.9 per cent of the stillbirths or infants dying in the neonatal period were examined post mortem by the obstetric pathologist. Complete autopsies were performed on 318 term, 319 viable premature, and 231 nonviable premature infants.

Results.—The four major causes of fetal and neonatal deaths as determined from this study was found to be (1) prematurity; (2) pulmonary lesions; (3) birth trauma; and (4) maceration, following antepartum or intrapartum fetal deaths, often of unknown cause (Fig. 1).

I. *Prematurity.*—This was found to be the greatest single cause of death (Fig. 1). In 27.6 per cent of all the autopsies it was felt that death occurred because the vital organs were insufficiently developed to carry on with the proper functioning necessary to maintain life. Considering the premature group of infants alone (viable and nonviable), the death rate from this cause

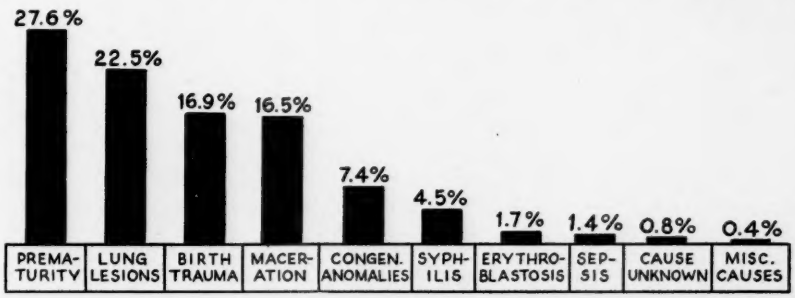

Fig. 1.—Causes of fetal and neonatal deaths, 868 autopsies.

TABLE I. FETAL DEATH RATE DURING A TEN-YEAR PERIOD BEGINNING JULY 1, 1933, AND ENDING MAY 31, 1943

Total Deliveries	16,669	
Total fetal and neonatal deaths	1,114	
Uncorrected fetal mortality		6.6%
Nonviable deaths	312	
Corrected fetal mortality (This figure includes macerated stillbirths and babies dying of congenital anomalies)		4.8%
Total autopsies performed	868	
Autopsy percentage rate		77.9%

TABLE II. CORRECTED DEATH RATE OF TERM AND PREMATURE INFANTS

YEAR	TERM DEATH RATE	PREMATURE DEATH RATE
June 1, 1934—May 31, 1935	92 (6.10%)	43 (63.2%)
June 1, 1935—May 31, 1936	48 (3.00%)	40 (49.3%)
June 1, 1936—May 31, 1937	34 (2.80%)	24 (39.3%)
June 1, 1937—May 31, 1938	21 (1.50%)	26 (44.0%)
June 1, 1938—May 31, 1939	9 (0.65%)	56 (35.8%)
June 1, 1939—May 31, 1940	11 (0.84%)	34 (15.5%)
June 1, 1940—May 31, 1941	12 (0.90%)	51 (40.5%)
June 1, 1941—May 31, 1942	12 (0.74%)	18 (12.2%)
June 1, 1942—May 31, 1943	18 (1.20%)	32 (17.3%)
Average death rate	1.97%	35.2%

Note: The above figures include macerated stillbirths and babies dying of congenital anomalies. The premature deaths exclude nonviable infants living a few hours.

was higher (43.6 per cent), while one-third of the viable premature infants failed to survive for similar reasons (Table III). Other statistical studies of fetal mortality have consistently reported prematurity as the most frequent cause of death.[5, 8, 11, 14]

TABLE III. CAUSE OF DEATH IN 319 VIABLE PREMATURE BABIES

	LUNG LESIONS		PER CENT OF TOTAL DEATHS
	NUMBER	PER CENT	
A. Prematurity	105		32.90
B. Pulmonary lesions	68		21.30
1. Massive aspiration of amniotic fluid	35	51.5	10.97
2. Pneumonia	25	36.7	7.80
a. Congenital	1 (4%)		
b. Aspiration	20 (80%)		
c. Bacterial—origin undetermined	4 (16%)		
3. Hemorrhage	4	5.9	1.25
4. Hyaline membrane	4	5.9	1.25
C. Birth trauma	41		12.80
D. Maceration	50		15.60
E. Congenital anomalies	21		6.50
F. Syphilis	20		6.20
G. Sepsis	7		2.20
H. Erythroblastosis	2		0.62 } 2.18
Probable erythroblastosis	5		1.56 }
I. Other causes—Malnutrition	1		0.30

This group represents a large number of infants to die from a single cause. At postmortem examination the only findings were those attributable to immature development of the vital organs of the body. The lungs have failed to develop sufficiently to allow for ready and adequate transmission of oxygen to support life. The immaturity of the lungs explains the persistent cyanosis after birth in spite of continuous oxygen administration.

The kidneys in the premature are not completely developed, and the absence of a full complement of well-formed glomeruli and tubules impedes the normal functioning power of these organs. In the fetus, glomerular development continues until about the thirty-fourth or thirty-sixth week of intrauterine life.

The mucosa of the gastrointestinal tract has not attained its full capacity of assimilation of food. The digestive glands are smaller and fewer in number. Careful attention in providing these infants with easily assimilable food in small quantities and at frequent intervals is essential to their survival, and requires expert supervision.

The temperature-regulating mechanism in the premature infant is extremely unstable. Attention is necessary to avoid excessive loss of body heat and to provide an environment which will maintain a normal body temperature. Because of the reduced or complete lack of immunity, these infants are subject to infections, and rigid precautions must be observed in order to prevent their occurrence.

In order to reduce the mortality rate from prematurity, it appears obvious that careful and intelligent attention must be given in the care of the premature after delivery. The best environment for these infants must be supplied under adequate supervision by specially trained personnel.[10, 19] Their care presents four major problems:

1. Maintenance of body temperature.
2. Prevention of cyanotic attacks.
3. Proper nutrition.
4. Prevention of infection.

From the above observations, obstetricians might be tempted to absolve themselves of all responsibility in handling premature infants and to throw the burden entirely upon the shoulders of the pediatricians. However, the obstetrician plays a vital role in the initial handling of these cases, and it is his responsibility to turn over the premature to the pediatrician in the best condition possible. Of paramount importance is the part that the obstetrician must play in the management of the pregnancy, labor, and delivery, and in the initiation of respirations immediately after birth.[18]

To effect a lowering of the death rate from prematurity in this group the obstetrician must attempt to delay the onset of labor as long as possible. Certainly no procedure should be instituted for the induction of labor without sufficient indications until a period in development has been reached which will give the fetus the best opportunity for survival after birth. Whenever feasible, maternal complications of the prenatal period, which are associated with a high incidence of premature births,[8] should be treated conservatively as long as the delay does not create a serious hazard to the mother.

The premature infant is susceptible to injury by the normal processes of labor tolerated without harm by the term fetus. Too frequent or too strong uterine contractions during labor may produce intracranial injury (cerebral or arachnoid hemorrhage). Scott[15] observed that the highest death rate in prematures occurred following a short labor with frequent strong contractions of the uterus, with consequent injury to the fetus. Excessive use of sedation must be avoided because of the depressive effect on the respiratory center.[12, 15] The use of oxytocics during labor should be condemned for very obvious reasons. Premature rupture of the membranes is associated with a higher mortality in the premature infant.[15] Artificial rupture of the fetal membranes is contraindicated in order to avoid direct pressure on the immaturely developed fetal skull.

The second stage of labor should be shortened. The strain on the fetal head by the pressure of a resistant pelvic floor should be eliminated by performing an episiotomy, and the delivery may be completed with low forceps.[8, 16] Twenty-five and eight-tenths per cent of the prematures (viable and nonviable) in this study, sustained birth trauma. An appreciable reduction in deaths from intracranial injury in these infants has been attained at Bellevue Hospital by applying such measures in the second stage with a view to reducing the forces to which the prematures are subjected at this time.[16] Other investigators have shown that the lowest mortality rate occurred in the group of premature infants delivered by forceps, the highest death rate in deliveries by version and breech extractions, and the second highest rate in spontaneous deliveries.[15]

Immediately after delivery, energetic measures must be taken to initiate respirations. The most important of these measures is adequate aspiration to ensure an unobstructed flow of air to the lungs.[1] This is particularly important if some fetal asphyxia occurred in utero resulting in the aspiration of amniotic fluid. Eleven per cent of the viable premature infants were found to have massive aspiration of amniotic fluid at autopsy. This degree of aspiration of amniotic fluid may be avoided, in many instances, by prompt delivery of the fetus when fetal distress is observed during the terminal stage of labor.

Since prematurity alone is the greatest cause of fetal and neonatal mortality, it appears obvious that any marked reduction in the gross neonatal mortality must be brought about by a reduction in premature births, or by reducing the number of deaths from prematurity.

Although prematurity alone accounted for 32.9 per cent of the deaths among viable infants, autopsy findings indicate that two-thirds of these infants showed additional pathologic conditions which developed either in utero

or in the neonatal period. Pulmonary lesions were found most frequently as a cause of death (21.3 per cent). The most frequent type of lung lesions encountered were massive aspiration of amniotic fluid and pneumonia. Hemorrhage and hyaline membrane of the lungs occurred in a smaller number of cases. The other major causes of death in this group is shown in Table III.

Death from pneumonia was found to be a great hazard of the neonatal period. Seven and eight-tenths per cent of the viable premature infants died of pneumonia contracted during the first month of life. Aspiration pneumonia resulting from the inhalation of foodstuff was the greatest single hazard. Eighty per cent of the pneumonia in the premature was of this type. That this hazard can be greatly reduced during the neonatal period by proper care is attested to by the fact that in Bellevue Hospital, death from this type of pneumonia has decreased markedly in recent years. Twenty premature infants died of aspiration pneumonia and 16 of these deaths occurred during the first three years of this ten-year period. In a similar manner, the number of cases of premature babies dying of sepsis has been reduced. The seven deaths from sepsis among the viable premature infants occurred during the first three years of this study. This reduction undoubtedly has been brought about by the strict observation of precautions by a trained personnel.

II. *Pulmonary Lesions.*—The second most frequent condition accounting for death was found in the lungs (22.5 per cent). (Fig. 1.) Among the group of term infants, these lesions constituted the commonest single cause of death found (39.3 per cent). (Table IV.) In the viable premature group 21.3 per

TABLE IV. CAUSE OF DEATH IN 318 TERM BABIES

	LUNG LESIONS		PER CENT OF TOTAL DEATHS
	NUMBER	PER CENT	
A. Pulmonary lesions	125		39.30
1. Massive aspiration of amniotic fluid	83	66.4	26.00
2. Pneumonia	26	20.8	8.17
a. Congenital	12 (46%)		
b. Aspiration	7 (27%)		
c. Bacterial—origin undetermined	7 (27%)		
3. Hemorrhage	15	12.0	4.70
4. Congenital cystic lung	1	0.8	0.30
B. Birth trauma	76		23.90
C. Maceration	56		17.60
D. Congenital anomalies	32		10.06
E. Syphilis	4		1.20
F. Sepsis	5		1.57
G. Erythroblastosis	6		1.88
Probable erythroblastosis	2		0.63
			2.51
H. Cause unknown	8		2.50
I. Other causes—Cerebrospinal meningitis	2		0.63
Epidermolysis bullosa	1		0.31

cent were found to have lung lesions of serious proportion. These findings are in agreement with the observations of others that the majority of fetal and neonatal deaths are respiratory in their clinical picture.[7]

Aspiration of amniotic fluid: in massive amounts was the type of lung lesion most frequently demonstrable at autopsy (60.2 per cent). (Fig. 2.) In the group of term babies this lesion accounted for 26 per cent of the total deaths, while in the viable premature group only 10.97 per cent showed this condition. The higher incidence of aspiration of amniotic fluid in the term baby is probably related to the greater incidence of fetal asphyxia accompaning longer and more difficult deliveries.

The gross appearance of the lungs does not present any characteristic features suggesting this condition. The lungs appear congested but otherwise normal in appearance, and often retain their capacity for floating when immersed in water. The presence of aspirated amniotic fluid can be detected only on microscopic examination of the lungs.

Normal amniotic fluid has a high cellular content derived from epithelial desquamation of the vernix caseosa of the fetal skin. Meconium droplets are also present. These elements are readily demonstrated in the sediment of a centrifuged specimen of amniotic fluid. When large amounts of amniotic fluid are aspirated into the lungs, these telltale flattened epidermoid cells and meconium droplets will be found in the alveolar spaces in large numbers. The extent of lung involvement depends upon the degree of aspiration. In massive aspiration of amniotic fluid most of the alveolar sacs are filled with the cellular remnants of the amniotic fluid. In cases of a moderate degree of aspiration, areas, very frequently in a lobular pattern, of normal uninvolved alveoli are found.

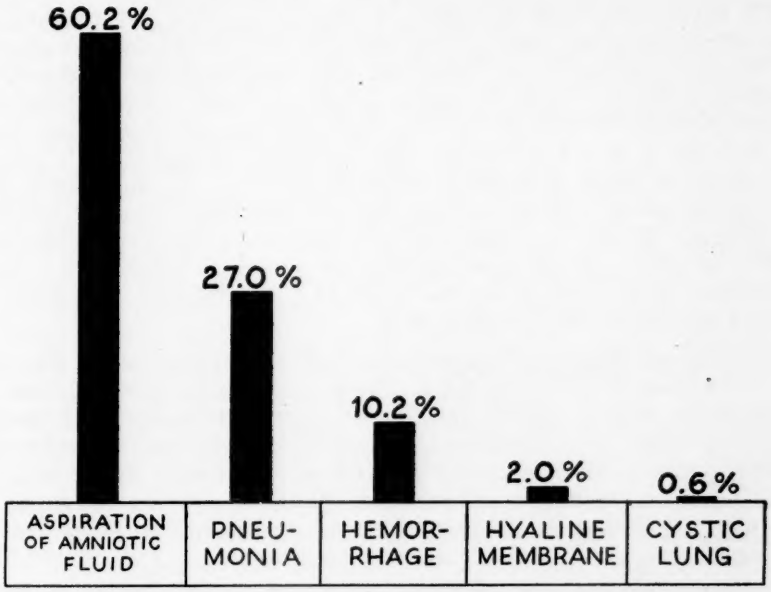

Fig. 2.—Types of lung lesions producing fetal or neonatal death.

A few scattered epidermoid cells frequently can be seen in the alveolae of infants who have died from other causes. These are usually derived from aspiration of amniotic fluid, which normally fills the trachea and upper bronchial passages, with the initiation of the first breath after birth. They cannot be regarded as having any serious significance.

Aspiration of large quantities of amniotic fluid occurs during intrauterine life as a result of an anoxic or asphyxial state in the fetus. Therefore, a discussion of this lesion must necessarily include some discussion of fetal anoxemia. Intrauterine asphyxia is known to produce physiologic and pathologic changes involving every organ and tissue in the body.[3, 7] The pathologic changes produced in the lungs have been described above. Should these infants survive birth, they present clinical features of respiratory difficulty. They appear extremely pale and flaccid with weak, slow heart action. Respirations are initiated with difficulty and, once established, these infants fre-

quently exhibit evidence of respiratory distress with labored, grunting respiration, dilatation of the alae nasi, and marked retraction of the costal margins. The cry is feeble, and varying degrees of cyanosis is present. Some of these clinical features may result from direct injury to the respiratory center by the asphyxia. The delay in establishing regular respiratory activity probably is due to injury to the center of respiration. However, the other clinical features may be explained by the direct effect on the functioning capacity of the lungs from massive or moderate aspiration of amniotic fluid.

The various causes of fetal asphyxia and the relative merits of the use of the terms anoxia, apnea, and asphyxia have been discussed by others.[1, 3, 6, 7, 13] Whatever the cause of the fetal asphyxia, the respiratory center is susceptible to the chemical changes produced by anoxia.[19] In the production of experimental anoxia, Eastman and Kreiselman[7] noted that the effect of mild degrees of anoxia was to increase the respiratory and cardiac heart rates. They explain this as a compensatory mechanism designed to supply the tissues with an adequate oxygen supply. This may explain the initial increase in the fetal heart rate above normal which occurs in early phases of fetal asphyxia. As the anoxic state continues, a stage of "oxygen crisis" is reached and the compensatory mechanism fails to supply sufficient amounts of oxygen to the tissues. Respirations stop and, following this, the heart rate is greatly slowed. Some such mechanism must occur in fetal asphyxia. The initial effect of respiratory stimulation caused by the anoxic state produces an increase in the rate and depth of intrauterine fetal respiratory movements[2, 17] causing the infant to aspirate large quantities of amniotic fluid. If the anoxic state continues, fetal intrauterine death occurs from irreversible damage to the central nervous system. Yant[20] has demonstrated that asphyxia results in congestion, perivascular edema, and hemorrhage into nerve tissue resulting in destruction of the neuron. Examination of the lungs in these infants will show evidence of extensive aspiration of amniotic fluid.

If intrauterine fetal death does not result from the anoxia, the aspiration of large quantities of amniotic fluid which occurred in utero as the result of the anoxic state will in itself prolong or aggravate a state of anoxia after birth. The alveolar sacs, distended by the aspirated fluid, are responsible for the clinical evidence of respiratory distress as previously described. In these cases, the massive aspiration of amniotic fluid is a major cause of death in that it causes a prolonged and fatal state of asphyxia similar to death caused by drowning.

The chance for survival of these infants is directly proportionate to the duration of the anoxic state, to the amount of amniotic fluid aspirated, and to the state of lung development. It appears obvious that a premature infant whose alveoli are immature will be more gravely embarrassed by a smaller degree of aspiration of amniotic fluid than a term baby. A fetus showing signs of intrauterine distress should be delivered as soon as conditions, compatible with the safety of the mother. permit. Prolonged fetal distress will not only result in aspiration of larger quantities of amniotic fluid, but will increase the danger from irreversible tissue damage to the central nervous system resulting from the anoxia.

Pneumonia: was the second most frequent type of lung lesion encountered at autopsy (27 per cent) (Fig. 2), accounting for 8 per cent of the total deaths in both the premature and the term groups of babies. However, in the term group, 20.8 per cent of the lung lesions were of this type, whereas in the viable premature babies its incidence increased to 36.7 per cent (Tables III and IV). Tyson,[19] in studying fetal mortality in Philadelphia, found that pneumonia was responsible for 5 per cent of the total mortality.

For purposes of classification, the types of pneumonia were found to fall into three different groups: (1) congenital pneumonia; (2) aspiration pneumonia, and (3) pneumonia of undetermined origin. *Congenital pneumonia* develops in the fetal lung during intrauterine life as the result of aspiration of amniotic fluid which has become infected, usually as a sequelae to premature rupture of the membranes. This is the type of pneumonia which occurs most frequently in the term infants (46 per cent). The train of events which leads to aspiration of infected amniotic fluid are the same as those which are followed by aspiration of noninfected fluid. *Aspiration pneumonia* resulting from inhalation of vomitus or food was seen most frequently among the premature infants. Eighty per cent of the pneumonias occurring among the viable premature babies were of this type. *Pneumonia of bacterial origin* occurred less frequently (20.8 per cent). The types seen were usually bronchopneumonia or a patchy disseminated bronchopneumonia. The incidence of this type of pneumonia was almost twice as frequent in the term babies as in the premature group.

Hemorrhage: was the third most frequently encountered lung lesion (10.2 per cent). Massive hemorrhage of the lungs accounted for 4.7 per cent of the deaths among the term infants and 1.25 per cent of the deaths among the viable premature group. Only the extensive forms of pulmonary hemorrhage were listed in this group. Mild patchy areas of hemorrhages frequently seen in premature infants or in association with intrauterine asphyxia were not considered of primary importance.

Massive pulmonary hemorrhage may develop if, with the occurrence of fetal asphyxia, respirations are initiated while the head is in the vaginal passages. During the passage of the head through the vagina, the mucous membrane is closely approximated to the mouth of the fetus. Attempts to breathe during this stage results in the production of a negative intrathoracic pressure. When all of the muscles of respiration come into play, the negative pressure becomes so great that engorgement of the alveoli takes place with subsequent rupture of the alveolar septa and blood vessels. This condition may also result from too energetic attempts at resusitation.

Hyaline Membrane: This lesion was seen in four premature infants (5.9 per cent). The exact etiology of this condition is unknown. Its formation may represent a late effect of intrauterine aspiration of amniotic fluid occurring well in advance of labor and delivery. In the succeeding antenatal period the fluid is absorbed but the solid elements of the aspirated amniotic fluid become altered to form a hyalinized gummy substance. This material blocks the opening of the alveolar sacs, prevents their expansion and is responsible for the dilatation of the alveolar ducts characteristic of this condition. This causes embarrassment to respiration, due to interference with the normal diffusion of gaseous elements in the alveolar spaces and to the inefficiency of such exchange through the walls of the alveolar ducts.

III. *Birth Trauma.*—The third largest cause of death was from birth trauma (16.9 per cent). Thirty-two and nine-tenths per cent of the term and 12.8 per cent of the viable premature infants died because of injury.

The types of injuries encountered were found to fall into three main groups: (1) intracranial; (2) spinal; and (3) intra-abdominal. In some instances, intracranial injuries were found associated with spinal or intra-abdominal injuries (Fig. 3).

The intracranial injuries consisted of lacerations of the dural septa. subdural hemorrhage usually due to rupture of the great cerebral vein or its tributaries, subarachnoid hemorrhages and subventricular hemorrhages. Lacerations of the dural septa (falx cerebri and tentorium) and subdural or subtentorial hemorrhages were the lesions most commonly found in the term

infant and were usually related to the performance of a difficult operative delivery. Subarachnoid and subventricular hemorrhages were characteristic of the lesions found in the premature infant. In contrast they were found frequently in babies born spontaneously. In babies of approximately thirty-four to thirty-eight weeks gestation, there frequently occurred combinations of the dural lesions seen in the term baby and the vascular lesions observed in the premature infant.

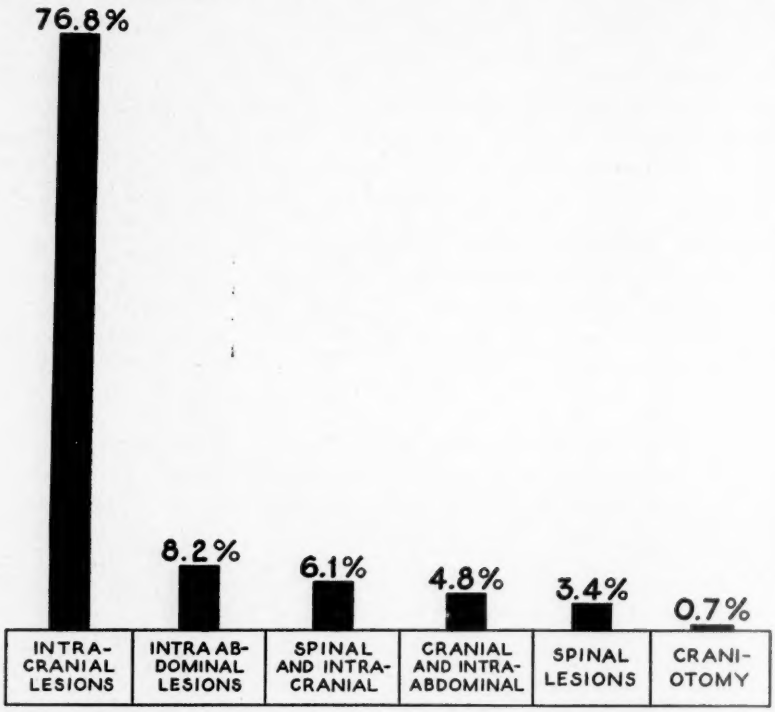

Fig. 3.—Types of birth trauma producing fetal death.

Spinal injuries involved the spinal cord, the vertebral column or both. These were more frequently combined with severe intracranial lesions. Most of the spinal injuries were limited to the cervical region, usually resulting in a fracture dislocation of the cervical vertebra and most frequently involving a separation of the epiphysis from the diaphysis between the sixth and seventh cervical vertebra. Occasionally disarticulation of the atlas and axis occurred. Following disarticulation of the vertebra, direct injury to the spinal cord may occur causing incomplete or complete cord lacerations. These injuries were usually sustained during delivery of the aftercoming head in breech presentations but occasionally during delivery of a large baby with impacted shoulders.

Intra-abdominal injuries were found to involve the liver, adrenals or kidneys and resulted from direct pressure on the abdomen during delivery of the breech or too strenuous force used in resusitation, particularly in the premature. The types of lesions observed were (1) rupture of the liver; (2) hemoperitoneum resulting from the rupture of a subcapsular hematoma of the liver; (3) hemorrhage into the adrenal medulla; and (4) hemorrhage into the kidney.

IV. *Maceration: Cause Unknown.*—A large group of the babies (16.5 per cent) autopsied were in a state of extensive maceration. Detailed anatomic dissection or microscopic study was impossible. In these cases, sections of the

vital organs were taken and stained with the Levitidi stain to determine the presence of spirochetes, and microscopic study of the bone was done to detect the presence of syphilitic osteochondritis.

An attempt has been made to correlate the death of the fetus and subsequent maceration with some clinical maternal disorder occurring during the prenatal period or labor (Fig. 4). In over one-half of the cases of maceration (55.2 per cent) no maternal cause for death of the fetus could be determined. Since most of these deaths occurred during the years before knowledge of the Rh factor, it is impossible to state whether some of these macerated stillbirths may have been due to erythoblastosis. In the remainder, however, some maternal abnormality was present. Toxemia was the most frequent maternal complication (21 per cent) which apparently resulted in death of the fetus in utero. Vaginal bleeding, most frequently due to premature separation of the placenta, was followed by death of the fetus and was the complicating prenatal factor in 11.8 per cent. Of the 46 macerated fetuses, born of mothers suffering from toxemia or premature separation of the placenta, 38 were premature.

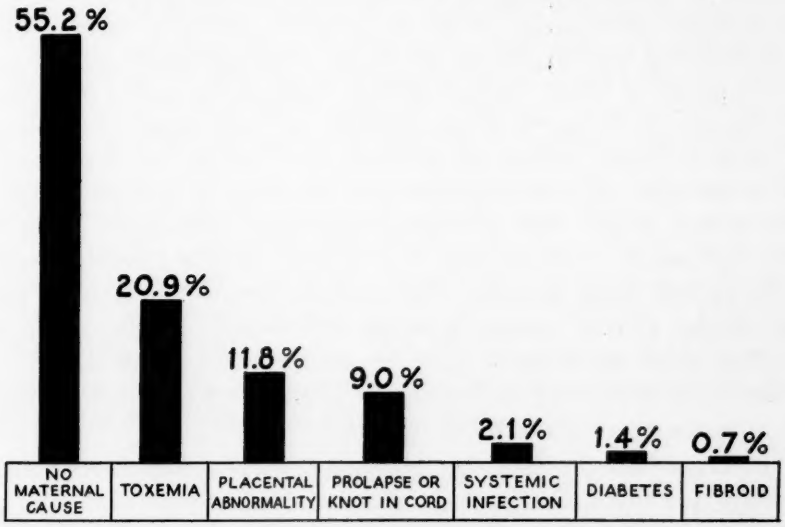

Fig. 4.—Complications of pregnancy associated with macerated stillbirths.

Obstruction of the umbilical cord by knots, prolapse or excessive winding about the fetus was found in 9.1 per cent of the cases of maceration and nine of these thirteen stillbirths were full term.

Rupture of the uterus (1 case), severe maternal infections (3 cases), fibromyomata uteri (1 case), and diabetes mellitus (2 cases) were among the remaining maternal conditions.

V. *Other Causes of Death.*—Space does not permit a detailed account of other causes of neonatal and fetal deaths. The incidence and the relative frequency of these conditions may be seen in the accompanying tables.

Comment

In recent years two studies of the causes of the fetal and neonatal deaths have been reported.[5, 11] Each of these included over one thousand fetal and neonatal deaths with postmortem examination performed in almost 90 per cent

of the cases. Anoxemia, prematurity, birth trauma, maceration, congenital anomalies and infections (mostly pneumonia) were listed as the main causes of death. Cruickshank[4] (1930) also found that 67.5 per cent of babies died of prematurity, asphyxia, and birth trauma; 29.7 per cent of infections; and 2.7 per cent of major congenital anomalies. Others have agreed that these lesions were the major causes of fetal and neonatal deaths.[15]

The present study confirms these findings, although due to differences in classification of the causes of death the findings appear to be at variance with these previous reports. We have attempted to avoid a mixture of physiologic and anatomico-pathologic terms in classifying the causes of neonatal deaths. Thus the term asphyxia, which denotes a physiologic state in utero, has been supplanted by anatomic terms describing the pathologic lesion which resulted from the asphyxial state and which was considered as being the major anatomic cause of death. Due to the asphyxia resulting from placental hemorrhage, prolapse of the cord or knot in the cord, maternal infection, or toxemia, deep inspiratory movements of the fetus are initiated in utero. As a direct result of this, the amniotic fluid contains many epithelial cells desquamated from the skin of the fetus. These cellular elements are found in large numbers in the lung alveoli and serve as the basis for the anatomic diagnosis of aspiration of amniotic fluid. Other minor anatomic evidences of the asphyxial state will be found also, such as congestion of all viscera and small hemorrhages of the brain and lungs. Not all asphyxiated babies will die in utero, but many of those that survive intrauterine life will die in the neonatal period as an aftermath of aspirated amniotic fluid which occurred in utero. Due to the flooding of the alveoli, proper gaseous interchange is impossible, and thus the asphyxial state beginning in utero continues in the neonatal period with the production of cyanosis and convulsions. The latter symptoms frequently lead to the erroneous diagnosis of birth trauma.

In the event that the amniotic fluid has become contaminated with a purulent exudate due to an amniotic sac infection, intrauterine asphyxia will result in the aspiration of infected amniotic fluid. Microscopically, examination of the lungs shows the alveoli to contain not only desquamated epithelial cells, but also large amounts of purulent exudate and many bacteria. Because this pneumonia originates while the fetus is in utero due to aspiration of infected amniotic fluid, this lesion has been termed a congenital pneumonia.

The term atelectasis has been avoided because it is not an anatomic cause of death.[1, 15] While it may be present, the underlying cause which results in this condition such as prematurity, birth trauma, and aspiration of foodstuff or vomitus should be considered the primary cause of death.

Table V has been prepared comparing our findings of the causes of fetal and neonatal deaths with those of two recent studies. The causes of death as reported in the preceding pages have been rearranged to conform with the nomenclature used by these authors. When this is done, the close similarity of the major causes of fetal and neonatal deaths in all three reports becomes apparent.

TABLE V. COMPARISON STUDIES OF NEONATAL MORTALITY

	POTTER AND ADAIR	D'ESOPO AND MARCHETTI	LABATE	
Prematurity	25.6	18.5	27.6	
Anoxia	28.7	19.8	17.9	(aspiration amniotic fluid 13.6%. Aspiration of infected amniotic fluid—congenital pneumonia 1.6. Hemorrhage of lung 2.3%. Hyaline membrane of lung 0.4%)
Birth trauma	13.0	11.6	16.9	
Maceration	17.2	18.7	16.5	
Major congenital anomalies	11.1	14.1	7.4	
Infections	4.7	8.1	6.1	
Erythroblastosis	2.5	2.8	1.7	
Syphilis	0.2	0.6	4.5	

An analysis of the causes of fetal and neonatal death is valueless unless conclusions can be drawn therefrom which will prevent fetal and neonatal deaths and thus improve the mortality rate. The death rates from prematurity, pulmonary lesions, and birth trauma, which constitute the three major causes of death, can be greatly improved. Similarly, fetal death from syphilis, infection, and erythroblastosis is preventable to a considerable degree.

Table II shows the reduction in the term and premature death rate at Bellevue Hospital during a nine year period. This decline in the death rate is largely due to the precautions which have been taken to prevent the occurrence of the major conditions which were found to have produced death of these infants. The lessons learned at the autopsy table have been carried to the delivery room and the nursery. The fetal and neonatal death rate for the country at large could be reduced equally well if the profession generally were to be made more conscious of the causes of this mortality.

Summary

1. An analysis of the cause of death has been made, based on the study of 868 autopsies performed during a ten-year period beginning July 1, 1933.

2. Prematurity, pulmonary lesions, and birth trauma were the three highest causes of death.

3. The main causes of fetal death in the term and premature infants and certain aspects of their prevention have been discussed.

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Discussion

DR. D. ANTHONY D'ESOPO.—Dr. Labate approached the subject of asphyxia from the point of view of the pathologist, and avoided the term asphyxia which Dr. Marchetti and I used in our paper. This was used synonymously with the term "aspiration of amniotic fluid." The diagnosis of aspiration of amniotic fluid can be made only from pathological study and since not all of our cases were examined postmortem, the clinical term, asphyxia, was used.

Dr. Labate's slide showing the pathology of aspiration of amniotic fluid was interesting and typical. There are other lesions that go with aspiration of amniotic fluid, or asphyxia, which I think should be stressed, namely, the marked congestion that takes place throughout the entire body of the infant; the blood vessels are dilated, and this is apparent not only macroscopically in the viscera, but also in all the microscopic sections. That point is interesting to me because recently in studying cases of birth injury we have been impressed with the frequency of the two conditions, namely, birth injury and asphyxia. I am sure that anybody who does newborn pathology will frequently see these two conditions associated. Sometimes it is difficult to tell which is the primary condition, that is, whether the child originally was subjected to birth trauma and as a result of that became asphyxiated, or whether the child was primarily anoxic and in the course of delivery was subjected to birth trauma. I wonder if the congestion, the marked engorgement of large blood vessels, which I think is such an important part of the associated pathology of anoxia, may not to a large extent contribute to birth trauma. Where there is marked engorgement or congestion of the vagina, injuries such as sulcus tears may easily occur with instrumental deliveries.

I wonder if the intracranial structures are not more easily injured when we have a baby who is suffering from anoxia. There is a tendency to rush the delivery of a child suffering from anoxia because of the fear that further anoxia will kill the baby. I believe that frequently in speeding the delivery we subject the baby to a considerable degree of trauma and as a result produce birth injuries.

DR. MORTIMER D. SPEISER.—It might be well to mention in connection with the prophylaxis of congenital pneumonia, the possible value of the routine employment of substances such as penicillin after the membranes are ruptured in order to avoid the consequences of congenital pneumonia.

MENSTRUAL TOXIN

I. Experimental Studies*

O. WATKINS SMITH, PH.D., BROOKLINE, MASS.
(From the Fearing Research Laboratory, Free Hospital for Women)

FROM the accumulated bulk of experimental evidence it appears clear that only two factors are essential for endometrial bleeding in the primate; an endometrium and withdrawal of hormonal support, either estrogen alone or estrogen and progesterone. The classical researches of Markee[1] on the behavior of blood vessels in intraocular transplants of monkey endometria and the histologic studies of Bartelmez[2] on human uteri have revealed profound and characteristic vascular changes to be constant and immediate precursors of endometrial bleeding. The sequence of these changes is the same whether the endometrium has been previously stimulated by estrogen alone or by estrogen and progesterone. In the final analysis, therefore, of all the theories on the cause of menstruation that have been proposed, the only one that still seems to hold is that of estrogen deprivation, first propounded by Edgar Allen in 1927.[3]

Nevertheless, a number of writers have questioned the adequacy of the withdrawal theory. Hartman and Firor[4] have raised numerous objections based upon their observations in monkeys. They feel that some extraovarian factor must be involved and, considering "the potency of infinitesimally minute quantities of chemical substances in their vasomotor action," have suggested that the answer may lie in the field of pharmacology rather than endocrinology. Engle[5] has voiced similar doubts and states that "it may be a mistake to say that the withdrawal of one of the hormones *causes* menstruation; rather such a lack of hormone *permits* changes in the endometrium and blood vessels, which result in the bleeding."

A similar line of thought led us to study the menstrual discharge itself with the idea that the "bleeding factor," if it existed, must originate locally and might be present in this material. Macht[6] had previously found in the sweat, saliva, and circulating blood of menstruating women a substance toxic to plant growth. No other scientific evidence had been reported, however, to indicate that menstruation might be a toxic phenomenon, although folklore from as far back as biblical times has considered it such.

The Toxicity of Menstrual Discharge

In our earliest work, published in 1940,[7] we first tested pooled specimens from a complete menstrual period, the whole unextracted discharge being used. For measuring toxicity the immature male rat (nineteen to twenty-one days old) was employed, and the smallest amount that caused death within forty-

*Presented on Jan. 25, 1947, at a conference on Menstruation and Its Disorders sponsored by the National Committee on Maternal Health.

eight hours of a single subcutaneous injection was considered the minimal lethal dose (M.L.D.). The toxicity of the total output for one period of young women with regular cycles and no excessive flowing was fairly uniform, the M.L.D. lying between 0.05 and 0.2 c.c. of whole discharge. It was soon discovered, however, that separate specimens from the same individual during a given menstrual period varied considerably. The greatest toxicity appeared to be in specimens collected early, when flow was scanty, and the least in specimens obtained when bleeding was profuse. Whole discharge from a patient with dysfunctional flowing could be shown to contain the toxin only if the material was concentrated by extraction (v.i.). The explanation for these observation was revealed when we began centrifuging the whole discharge and testing separately the supernatant "serum," the bottom layer of red blood cells, and the middle grayish layer containing endometrial debris. The washed red blood cells were found to be practically nontoxic, whereas the "serum" from a normal menstruation was always lethal in 0.1 to 2 c.c. amounts, and the washed endometrial debris, suspended in saline for injection, contained the greatest concentration of the toxin, being lethal in amounts equivalent to 0.005 to 0.1 c.c. The toxicity of various specimens of whole discharge was then discovered to be directly proportional to the amount of endometrial debris, specimens collected during scanty flow at the start of menstruation containing the greatest proportional amounts of debris, and those from cases of dysfunctional flowing containing the least. It appeared, therefore, that the endometrial debris was the source of the toxin. This was confirmed by the demonstration that fresh endometrium obtained directly from the uterus just before or during menstruation was lethal to rats in 50 to 100 mg. amounts (wet weight), whereas 200 to 300 mg. of endometrium taken at other times were nontoxic. The concept was tenable, therefore, that the premenstrual withdrawal of hormonal support permits catabolic changes in the endometrium which result in the formation or release of a highly toxic material. The variability in the amount of endometrial debris, and of toxicity, in various specimens indicated that postovulatory flow was associated with a more profuse release of toxin and shedding of endometrial tissue than pertained when bleeding was the result of estrogen withdrawal only. From this we would conclude that, although estrogen deprivation causes release of the same toxic factor as that present at postovulatory bleeding, previous stimulation of the endometrium by progesterone results in release of larger amounts of toxin.

Extraction of Toxin from Menstrual Discharge

In concentrating the toxic factor from menstrual "serum" or whole discharge, we used fractional salting-out with $(NH_4)_2SO_4$ and found that all of the toxicity was recovered in the water-insoluble portion after dialysis of the euglobulin precipitate that was brought down by one-third saturation with $(NH_4)_2SO_4$. We observed that this precipitate was not entirely soluble in physiologic saline, as are normal serum euglobulins, and that if the saline suspension was centrifuged until the supernatant was clear, all of the toxicity was

concentrated in the saline-insoluble precipitate. We therefore concluded that the toxic factor either was, or was closely associated with, an atypical euglobulin. Saline suspensions of the water-insoluble precipitate after dialysis were used for tests, and, when fresh, were lethal in amounts equivalent to the M.L.D. of the original "serum" or whole discharge. This is the method still used by us for concentrating menstrual toxin. The toxic factor, however, is extremely labile, especially after this partial purification. It is destroyed by prolonged dialysis (over seven hours against running tap water), by hydrogen ion concentrations above seven or below six, by temperatures above 45° C., and by organic solvents sufficient to precipitate proteins. In aqueous suspension toxicity disappears fairly rapidly, even if kept at temperatures below freezing. The only means by which the original toxicity of unextracted menstrual "serum," of whole discharge or of euglobulin precipitates may be preserved is by immediate and rapid freeze-drying.

Specificity of the Toxin of Menstrual Discharge

Hemolysis is always quite pronounced in menstrual discharge. The possibility that toxicity might be due to products of hemolysis, however, was eliminated by the demonstration that toxicity comparable with that of menstrual "serum" could not be produced by hemolysis of the red blood cells of the same specimen. Furthermore, repeated washings of the endometrial debris of menstrual discharge with physiologic saline until all the color of hemoglobin was removed did not decrease the very marked toxicity of this fraction. The possibility that bacterial contamination accounted for toxicity was, of course, considered. If bacterial action were involved, one would expect an increase in toxicity upon standing at room temperature. Early in our investigations, however, it was discovered that unless each collection was refrigerated immediately, toxicity would disappear rapidly. Furthermore, sterile scrapings of menstruating endometrium gave the typical reaction and death in test animals. Finally, the incubation of normal venous serum inoculated with menstrual discharge did not produce toxicity comparable with that of the discharge itself.

Because the evidence seemed to us sufficient to rule out bacteria, alive or dead, as responsible for the toxicity of menstrual discharge, it was not until recently that we tested the effect of Seitz filtration. The "serum" of menstrual discharge is a thick, viscous fluid which, even after prolonged centrifugation, is never clear. Because of its content of mucoid material, it can be filtered only through a fast filter paper, giving a cloudy filtrate. From a 60 c.c. sample of "serum" we were able to get only 10 c.c. through a Seitz filter. What came through was thin, crystal clear, and nontoxic in five times the M.L.D. of the original discharge. In attempting to concentrate this filtered "serum" we were surprised to discover that no precipitate came down upon one-third saturation with $(NH_4)_2SO_4$. The "serum" from centrifuged discharge gives a very heavy precipitate at this point, much more than is obtained by one-third saturation of venous serum. This observation leads us to wonder if the toxin of menstrual discharge may not be contained in or adsorbed upon a suspended protein aggregate. Since the removal of this aggregate by Seitz filtration also

removes the euglobulins that may be precipitated by one-third saturation with $(NH_4)_2SO_4$ as well as the toxin, we may still be correct in assuming that the toxin is a large moleculed, euglobulin-like material. It differs from the euglobulins of normal serum, however, in that it is insoluble in physiological saline. From the previously observed findings, we feel sure that bacteria are not responsible for the toxicity of menstrual discharge, and the very fact that Seitz filtration removes the toxic factor argues against the possibility that toxic products of bacterial action are involved.

The Pathologic Action of Menstrual Toxin

The pathological effect of menstrual toxin upon the immature rat is one of generalized tissue and pronounced vascular damage.[7, 8] The injection is given subcutaneously in the nape of the neck. Within twelve hours the animal shows a bloody discharge from the eyes and the nose and a pronounced girdle of edema through the chest and axillary region. Within twenty-four hours the animal is usually "dead on its feet," but may keep breathing for another ten to twenty hours if a minimal lethal dose has been injected. Autopsy at this time reveals bloody edema throughout the axillary region, a mottled appearance in the liver, swollen, pale kidneys, and enlarged, purple adrenals, these being the most characteristic, grossly-apparent abnormalities. The urine is always concentrated, indicating water retention, and sometimes bloody. Doctor Arthur T. Hertig has kindly consented to discuss the microscopic pathology resulting from menstrual toxin at the end of our papers. That the pathologic changes are the result of vasoconstriction and local stasis is indicated by the fact that the intracutaneous injection of tiny amounts of the toxin into rabbits prevents the appearance of intravenously administered trypan blue in that area, and keeps the dye from diffusing from that area if it is intracutaneously administered there. The menstrual process as actually observed by Markee in endometrial transplants into the monkey's eye suggests the local release of some vasoconstrictor material. In fact, Markee[9] has recently demonstrated that a so-called "necrosin-like" substance similar to if not identical with our menstrual toxin (v.i.) causes constriction of the coiled arteries in intraocular endometrial transplants and concludes that the vasoconstriction which begins four to twenty-four hours before the start of bleeding and persists throughout it is controlled by such a substance.

Menstrual Toxin and Canine "Necrosin"

The fact that the toxin of menstrual discharge appeared to be derived from the cast-off endometrium indicated that it might be a product of the tissue catabolism which results from withdrawal of hormonal support. Throughout our studies we have been imbued with the idea that tissue catabolism from causes other than hormonal and in sites other than the endometrium might involve the release of a similar toxin. Negative results were acquired in our numerous attempts to recover a toxic protein from various parts of the anatomy of rats, rabbits, and guinea pigs after partial blocking of the circulation. One of the reasons why we were anxious to obtain the toxic factor from other than

human sources was because we had shown that immunity to menstrual toxin could be produced by repeated injections of sublethal amounts, and that the serum of an immunized rabbit prevented death in a rat given an M.L.D. of toxin.[8] We were thinking of this in relation to the treatment of late pregnancy toxemia, since we already had reason to believe that the same toxin was operative in this disease. Serum from a rabbit immunized against menstrual toxin could not, of course, be given to human beings because of the content of nonspecific antibodies to human protein. The production of the same toxin in other species, therefore, had practical possibilities from the clinical aspect.

While we were engaged in studies along this line, a preliminary report by Menkin appeared in *Science*[10] describing an injury factor in the pleural exudate of dogs following the inflammatory reaction caused by turpentine. Many points of similarity between his so-called "necrosin" and our menstrual "toxin" suggested that we were dealing with the same material. Among others, "necrosin" was very labile and concentrated in the euglobulin fraction, being, however, an atypical euglobulin, since it was not soluble in the presence of electrolytes. In attempting to prepare necrosin ourselves according to Menkin's specifications, we discovered that the euglobulin fraction of canine pleural exudate frequently has no demonstrable amount of toxicity, by our test, and never contains concentrations that compare with those in menstrual discharge. However, by fractionation of this material we were able to get enough to perform experiments which gave good indication that canine pleural exudates and human menstrual discharge contain an identical toxic factor. The pathologic effects of necrosin were found to be entirely similar to those of menstrual toxin, although much more pleural exudate must be used to demonstrate toxicity in rats.[11] The euglobulin fraction of menstrual discharge is markedly fibrinolytic as well as toxic.[11-13] We found canine "necrosin" also to have this property,[11, 12] and Menkin gives reference to unpublished findings of his own which confirm this.[14] The pyrogenicity of the euglobulin fraction of canine pleural exudate as tested on rabbits[14] was also demonstrable with menstrual toxin.[11] We have been unable to separate the pyrogenic factor from the toxin of menstrual discharge, although Dr. Menkin believes that in pleural exudate they are different entities. Our own feeling is that the elevation of temperature observed in the rabbit is the usual response of that species to nonspecific, injurious stimuli. We have been unable to affect the body temperature of rats or guinea pigs with either "necrosin" or menstrual toxin. In the pseudoglobulin fraction of menstrual discharge we have found a factor capable of prolonging the survival time of rats given a lethal dose of menstrual toxin.[11] We discovered that this same fraction protects rats against canine "necrosin" and that the pseudoglobulin fraction of pleural exudates, both human and canine, protects against menstrual toxin.[11, 15] This finding has had practical implications which will be discussed further.

The most direct evidence for the similarity of the toxic protein of menstrual discharge and of canine pleural exudate has been gained by immunologic experiments. Neither menstrual toxin nor Menkin's "necrosin" have been suf-

ficiently purified so that nonspecific human and canine proteins, respectively, have been eliminated. The fact that both produce the formation of precipitin antibodies against themselves, therefore, is without significance. The demonstration, however, that the serum of a rabbit immunized against menstrual toxin precipitates canine "necrosin" and vice versa supplies strong evidence for an identical protein factor in these two materials.[11] These cross precipitin experiments were few in number and require further confirmation. Recently we have been attempting to do this, but have had considerable difficulty in recovering enough necrosin from canine pleural exudates to produce a high enough titer of antibodies to give clear-cut results. For this same reason, our original hope that necrosin-immune rabbit serum would provide an antitoxin for menstrual toxin that was free of nonspecific antibodies to human proteins has had to be abandoned. Unless the precipitin antibody titer is as high as 1:1,000,000, transferable immunity is not demonstrable. This we have never been able to acquire in necrosin-treated rabbits, although such a titer against menstrual toxin is easily produced. As stated above, the serum of an animal thus immunized against menstrual toxin protects an immature rat against an otherwise lethal dose of menstrual toxin. The same serum affords equally good protection against a lethal dose of canine necrosin.

The apparent identity of the product of endometrial breakdown after withdrawal of hormonal support with a protein substance released from cellular injury related to an inflammatory process strengthens the concept that tissue catabolism from various causes may involve the production or release of such a toxin, thus relating this factor, possibly, to the clinical syndrome of burns, crush syndrome, shock, postoperative morbidity, etc., as well as late pregnancy toxemia, the various clinical pictures depending upon the amount and duration of formation and absorption of toxin. The fibrinolytic activity of menstrual discharge suggested to us that the toxin might be an intermediary product of the action of a proteolytic enzyme released by tissue injury. We now have reason to believe, however, that toxin and enzyme may be identical. Possibly the toxin and/or enzyme and the protective pseudoglobulin are split-off components of cells in the process of tissue catabolism.

Menstrual Toxin in the Circulating Blood

Early experiments convinced us that there was not enough toxin in the circulating blood at the time of menstruation to be demonstrable by our test for the lethal action in immature rats. Our more recently studies of the characteristics of menstrual discharge supplied us with more sensitive tests, and we have found that the circulating blood of normal women at the time of menstruation differs from that collected between catamenia and resembles menstrual discharge in that it contains, in the euglobulin fraction, fibrinolytic and pyrogenic activity (as tested on rabbits) and, in the pseudoglobulin fraction, a substance capable of prolonging the survival time of rats given a minimal lethal dose of menstrual toxin.[15] We have also found these same properties to characterize the venous blood of pregnant women suffering from late pregnancy tox-

emia.[15] In the serum of normally pregnant women they are demonstrable only during labor. Our few observations on the presence of precipitin antibodies to canine necrosin immune rabbit serum in the circulating blood of menstruating and toxemic women[15] require further confirmation. The fibrinolytic activity of venous serum of toxemic as opposed to normal pregnancies has recently been confirmed by Willson and Munnell.[16]

Since our last publication on the subject,[11, 15] we have continued testing various types of circulating blood for fibrinolytic enzyme, utilizing the method in which the euglobulins from 5 c.c. of serum are concentrated for test against a standard fibrin clot.[15] An essential part of this method is establishing the smallest amount of fibrinogen and thrombin in the preparations used which, in the absence of any added fibrinolysin, will give a clot that remains stable during the twenty-four-hour incubation period. A control must be run for each series of observations. Previously unpublished results on untreated women are summarized in Table I. Our earlier observations are confirmed and it is apparent that the presence of the enzyme is associated with cellular injury from causes other than hormonal, as, for example, infectious, cancer and postoperative morbidity. The most striking results have been with sera from women suffering from pre-eclampsia and eclampsia and in specimens collected at delivery after a prolonged labor.

TABLE I. FIBRINOLYTIC ENZYME IN THE CIRCULATING BLOOD OF WOMEN

CONDITION OF PATIENT	NUMBER OF PATIENTS	NUMBER OF SERA	DISSOLUTION OF FIBRIN CLOT % OF TESTS SHOWING: COMPLETE	PARTIAL	NONE
A. Nonpregnant					
Normal—not flowing	11	17	0	0	100
Flowing {Normal cta.	6	10	13	87	0
Flowing {Pathologic	5	5			
Infections (pelvic abscesses, etc.)	5	6	0	83	17
Invasive cancer (not flowing)	3	3	0	100	0
Prolapse of uterus {before operation	3	3	0	0	100
Prolapse of uterus {2 days postoperative	3	3	0	100	0
B. Pregnant—During Second or Third Trimester					
Pregnancy normal	6	13	0	0	100
Pre-eclampsia or eclampsia	11	24	71	29	0
C. Pregnant—at Delivery					
Elective Cesarean	5	5	0	0	100
Spontaneous labor (1-7°)	3	3	0	0	100
Induced labor (2-5°)	3	3	33	67	0
Spontaneous labor (18-39°)	4	4	100	0	0

In the studies on blood at delivery we also ran determinations upon the fetal blood, i.e., blood collected from the umbilical vein and artery (Table II). These are of interest in connection with the possible mechanism of formation and release of the enzyme. Fibrinolytic activity was more marked in the arterial than in the venous umbilical blood and bore no constant relationship to the amount of circulating enzyme in the mother. Thus, in elective cesarean sections no activity was demonstrable in the maternal blood, whereas the tests on fetal blood were all positive. In other words, the enzyme in the fetal circulation ap-

pears to originate in the fetus and the observations suggest that it is proportional to the degree of anoxemia. Furthermore, the pseudoglobulin fraction of fetal blood is markedly protective against menstrual toxin.

TABLE II. FIBRINOLYTIC ENZYME IN MATERNAL VS. FETAL SERUM AT TIME OF DELIVERY*

	MATERNAL		FETAL			
			VENOUS		ARTERIAL	
	NUMBER SERA	PER CENT POSITIVE	NUMBER SERA	PER CENT POSITIVE	NUMBER SERA	PER CENT POSITIVE
Spontaneous labor 1-7 hours	3	0	3	0	3	67
Induced labor 2-5 hours	3	100	3	67	3	67
Spontaneous labor 18-39 hours	4	100	4	75	4	100
Elective cesarean no labor	5	0	5	100	4	100

*These experiments were performed in collaboration with Drs. Clement A. Smith, Duncan E. Reid and Charles C. Robey of the Boston Lying-In Hospital, Dr. Robey having collected the maternal and fetal bloods for study.

Are Toxin and Enzyme Identical?

Although quantitative tests have not been performed, the amount of enzyme appears to be roughly proportional to the amount of toxin present in the material tested. As little as 0.005 c.c. of unextracted "serum" from menstrual discharge will give complete dissolution of a fibrin clot in twenty-four hours; whereas more pleural exudate is required and the serum of circulating blood has to be concentrated in order to give a positive test by this method. The fibrinolytic activity of the blood of patients with late pregnancy toxemia is, in general, more marked than that in the circulating blood of menstruating women (Table I), and appears to be related to the severity of the disease. Furthermore, the administration of the protective pseudoglobulin to both pregnant and nonpregnant patients whose blood contains fibrinolytic activity causes a marked reduction or disappearance of the enzyme, this effect being associated with alleviation of toxic signs. Further details on this subject will be presented by Dr. George V. Smith. These observations have led us to wonder if enzyme and toxin may not be identical. On the other hand, human plasma treated with chloroform according to the method of Tagnon and Taylor[17] is as markedly fibrinolytic as menstrual discharge, but contains no demonstrable amount of toxicity. (It also contains no protective pseudoglobulin, much to our disappointment.)

Source of the Protective Factor for Clinical Trials

The most practical as well as the richest source of this factor has been human exudative material from any inflammatory process. During the last eight months we have obtained from eight patients with metastatic carcinoma nearly 70 liters of pleural or abdominal fluid. The pseudoglobulins have been partially purified and concentrated by fractional salting out with $(NH_4)_2SO_4$, and the final preparation passed through a Seitz filter into sterile vials. This

relatively crude method of preparation gives good yields of the protective factor in a slightly cloudy, greenish fluid, which, although some preparations cause local soreness, has never produced any systemic reactions when intramuscularly injected. We would like to concentrate and purify this factor further, both for clinical purposes and with the aim of learning more about the nature of this substance.

The Pituitary Stimulating Properties of Menstrual Toxin

In our earliest work on menstrual discharge it was discovered that this material stimulated the production of functional corpora lutea in mature female rats,[18] as well as causing pronounced adrenal enlargement.[7] This finding was not emphasized, since we were later informed by Dr. E. B. Astwood that he, in unpublished work, had observed the same phenomenon as a result of any injurious stimulation. Various investigators have confirmed Selye's[19] original observation of adrenal enlargement in rats following noxious stimuli, and have shown this reaction to be mediated by the pituitary. So far as we know, however, Dr. Astwood and ourselves are the only observers who have noted the stimulation and release of gonadotropic as well as adrenotropic hormones from the pituitary as a part of the "alarm" reaction. This effect has been recently confirmed by experiments upon mature male rats whose adrenals and pituitaries were weighed following injections, and the pituitaries transplanted into immature females to test their content of adrenotropic and gonadotropic hormones (Table III). The administration in a single injection of an amount of toxin sufficient to kill these animals caused an immediate enlargement of the adrenals but no demonstrable effect upon the pituitaries, except a questionably significant decrease of adrenotropic activity. The daily administration for three days of an amount that produced very little clinically apparent toxic

TABLE III. EFFECT OF MENSTRUAL TOXIN UPON THE ADRENALS AND PITUITARIES OF INTACT MATURE MALE RATS

ADMINISTRATION OF TOXIN*	AUTOPSY HOURS AFTER LAST INJECTION	NUMBER OF RATS	AVERAGE PER CENT CHANGE VS. LITTERMATE CONTROL†			
			ADRENALS WEIGHT	PITUITARY WEIGHT	TRANSPLANTABLE ACT. OF PIT.‡ ADRENOTROPIC	TRANSPLANTABLE ACT. OF PIT.‡ GONADOTROPIC
(1) 400 mg. in 1 injection	24°	4	+64 ± 10	+1.3 ± 2	−10 ± 3	+0.5 ± 2
(2) 100 mg. in 6 injections over 3 days	16°	4	+0.5 ± 4	+9.7 ± 3	−21 ± 2	−37 ± 5
(3) 400 mg. in 10 injections over 5 days	16°	5	+52 ± 9	+21 ± 2	−22 ± 4	+42 ± 5
Control rats (littermate vs. littermate)		10	+2.1 ± 3	+0.9 ± 4	−1.7 ± 4	+0.7 ± 2

*Seventy-five mg. = M. L. D. for 19d., 25 Gm. male rats. The animals in group (1) were moribund at autopsy; those in group (2) were well except for slight subcutaneous induration at the site of injections; those in group (3) had lost weight, were apathetic and had severe local reactions at the site of injections.

†For each experimental animal a control littermate of the same weight (± 5 Gm. was simultaneously autopsied. All animals were 80 to 100 days old and weighed 150 to 200 Gm.

‡Pituitaries were ground in saline and injected in 6 injections over 3 days into 19- to 21-day-old female rats whose ovaries and adrenals were weighed on the 5th day. For each experimental pituitary recipient, a control littermate of the same weight was run that received the pituitary of an uninjected littermate donor.

reaction had no effect on adrenal or pituitary weights, but caused a significant decrease in the transplantable adrenotropic and gonadotropic activity of the pituitaries, indicating release of both of these factors. When a toxic but sublethal daily dosage was given for five days, enlargement of the pituitaries as well as of the adrenals resulted, together with a decrease in transplantable adrenotropic activity and an increase in the content of gonadotropic hormone. From these observations it would appear that menstrual toxin (and probably any noxious stimulation) may, in a single overwhelming dose, have a direct effect upon adrenal weight. In sublethal dosages over longer periods, pituitary gonadotropic as well as adrenotropic activity is influenced, the indications being that both release and increased stimulation of gonadotropic activity may result, the type of response being dependant upon the amount given and the duration of treatment. These findings seem to us to give the "adaptation reaction" even more physiologic significance than is ordinarily attributed to it, since the reproductive organs as well as the adrenals appear to be influenced.

Conclusion

Although the studies on menstrual toxin that I have presented cover a period of eight years, it is apparent that much work remains to be done. Certain properties of menstrual discharge have been established, the most important being a toxic factor and a fibrinolytic enzyme associated with the euglobulin fraction, and a substance in the pseudoglobulin fraction which neutralizes the toxin. These same properties have been demonstrated in the circulating blood of women during menstruation, late pregnancy toxemia and prolonged labor but not in that of nonmenstruating or normally pregnant women. They have also been demonstrated in exudative material from inflammatory reactions, indicating that, although in the menstruating endometrium and in toxemia of pregnancy they result from tissue catabolism due to withdrawal of hormonal support, other sorts of cellular injury may cause a similar phenomenon. At present, however, they can only be called "properties," since neither the mechanism of their formation, other than that it appears to be a part of tissue catabolism, nor their chemical nature, other than that they are associated with protein materials, has been established. Thus far we have only been scratching the surface in an attempt to gain some further understanding of menstruation and of late pregnancy toxemia and in the hope of gaining knowledge that would be of clinical value. We would be delighted if the pathologists, the immunologists and the protein chemists would consider our pioneering efforts worthy of their more refined methods of investigation.

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MENSTRUAL TOXIN

II. Clinical Significance*

GEORGE VAN S. SMITH, M.D., BROOKLINE, MASS.
(From the Fearing Research Laboratory, Free Hospital for Women)

THE finding of a toxic protein in the menstruating endometrium constitutes a point of departure both for explaining the local and systemic phenomena related to menstruation, for investigating processes similarly preceded by withdrawal of estrogen and progesterone, and involving endometrial damage such as labor and the various types of pathologic pregnancy and for the study of other conditions in which injury of tissue is involved. Furthermore, it constitutes a basis for the development of treatment not only of disturbances associated with the premenstrual, menstruating, and pregnant uterus, but also of pathologic states resulting from many other varieties of tissue damage.

O. W. Smith has shown that the atypical euglobulin derived from the endometrium during its late stages of retrogression is experimentally a powerful tissue-damaging agent, capable also of inducing endocrine changes indicative of increased secretion and release of gonadotropic as well as adrenotropic hormone. She has also shown by immunologic studies, which require further investigation and confirmation, that this menstrual toxin and Menkin's canine necrosin are probably identical, thereby bringing into close relationship tissue damage in two species and from different causes. She has demonstrated fibrinolytic activity to be closely associated with menstrual toxin and canine necrosin, and has found fibrinolysin in the circulating blood during menstruation, labor, and toxemia of pregnancy, and following surgery and also in human pleural and peritoneal exudates. Furthermore, she has discovered that the pseudoglobulin fractions of all these fibrinolysin-containing fluids, with the exception of the circulating blood following surgery, which she has not yet tested, have the property of prolonging the survival time, and even occasionally of saving the lives, of immature rats given minimal lethal doses of menstrual toxin. This property requires painstaking, controlled experiments for its demonstration. Concentration of the pseudoglobulins is necessary. Protection appears to be a matter of quantitatively neutralizing the toxin and not of antibody formation in the ordinary immunologic sense.

I. Menstrual Toxin and the Local and Systemic Phenomena Related to Menstruation

The many and varied symptoms associated with menstruation and the other intangible concomitants of the process, such as changes in behavior, efficiency, etc., need not here be recounted. Suffice it to state that they all

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reflect constitutional as well as local disturbance of greater or lesser degree. This conclusion is confirmed by the objective findings, both local and systemic, such as: uterine congestion, uterine contraction—even tetanic contraction, pelvic congestion, systemic retention of water, increased fragility of skin capillaries, exaggeration of dermatologic lesions, congestion of mucous membranes, changes in intestinal activity, exaggeration of cerebrospinal disorders, and changes as in the encephalogram. The pathologic physiology of these tangible concomitants of menstruation seems best explained on the basis of mild vascular insult resulting in congestion and stasis and mild damage, i.e., irritation, of other tissues as expressed by changes in the activity of muscles, mucous membranes, nerves, and skin. In other words, the pathologic physiology may be considered similar to that which takes place in the endometrium prior to the stage of vascular rupture and tissue necrosis. From the information already available, we are postulating that all the signs and symptoms related to menstruation are ascribable to the action of the menstrual toxin, with the possible exception of some engorgement and soreness of the breasts. The most obvious confirmation of this hypothesis lies in the repeated clinical observation that women with nonpathologic ovaries and without any endometrium have no symptoms indicative of ovarian hormone withdrawal except that some complain of periodic or aperiodic soreness of the breasts. It remains to be proved that these women with ovaries and without endometrium have none of the objective signs of ovarian hormone withdrawal just enumerated, but Thorn and Emerson,[1] in a careful study of water balance in one such patient, found one sign absent, namely, the retention of water consequent upon the drop of urinary estrogen.

Once shedding of the endometrium is under way, diuresis occurs and the menstrual molimina usually disappear or become milder, due, we think, to removal of the source of the toxin. In further support of our hypothesis is the usual absence of menstrual molimina in patients flowing from a proliferative endometrium, and in their endometrium and discharge O. W. Smith has found less toxin.

There is one more objective systemic finding that deserves mention, though its significance is still unknown, namely, a drop of serum diastase during the forty-eight hours before menstruation.[2] On the basis of circumstantial evidence, we have guessed that this might reflect increased activity of the adrenal cortex, a reaction which, according to our findings, would be expected to result from menstrual toxin.

We think that the amount and duration of endometrial bleeding depend on the amount and rate of formation of the toxin and whether it is formed focally or diffusely, these variables depending, in turn, upon hormonal balance and vascular behavior. The exaggeration of menstrual molimina termed premenstrual tension we would attribute to prolonged absorption of the toxin from a secretory endometrium before its disintegration. The spasm of primary dysmenorrhea we think is an exaggerated local effect of the toxin. To test this assumption we have thus far injected the protective pseudoglobulin intra-

muscularly into four patients with primary dysmenorrhea, one of these patients having received it at the start of three different periods. Although relief or prevention of cramps seemed to result if the material was given within two hours of the start of flow, no conclusions can, of course, be drawn as to its clinical value on the basis of this subjective evidence.

Of more immediate significance were the studies of circulating fibrinolysin in three of these patients, namely, a reduction of the enzyme two hours after injection of the pseudoglobulin and its absence when the serum was tested eighteen hours later. One patient's serum was tested fifty-two hours later and again showed fibrinolytic activity. These tests were all run during the first three days of menstruation, at which time we have always found fibrinolytic activity in the serum of untreated women. Three of these patients volunteered the information that their flowing was more profuse than usual, an effect consistent with vascular and myometrial relaxation from partial neutralization of the toxin. The findings in these preliminary therapeutic trials constitute further circumstantial evidence in support of the concept that essentially all the menstrual phenomena do stem from the endometrium and are manifestations of local and systemic effects of the toxin. Moreover, the presence of the protective pseudoglobulin in the circulation during the catamenia is significant, since fluids in which toxin is found also contain this substance.

Our inability to demonstrate circulating toxin by tests with immature rats we attribute to the small quantities present. When larger volumes of serum are fractionated, the tests for toxicity become confusing because of nonspecific effects from the injection of larger amounts of protein. At this point one wonders why the protective pseudoglobulin already in the circulation during menstruation does not neutralize the toxin and reduce the fibrinolysin. We are at a loss to explain this paradox, unless we assume that the protective effect is the result of processing the serum. Protection with the serum of menstruating women is demonstrable only after removal of the euglobulin fraction. We have thought that this was due to the necessity of removing the fibrinolytic enzyme and toxin, but the possibility remains that some change in serum protein is effected which produces the protective factor. Even if this is the explanation, the precursors of this factor are apparently associated with the enzyme and toxin, since pseudoglobulin fractions of materials lacking in these properties are also lacking in protective action.

If the protective pseudoglobulin can be prepared in sufficient, concentrated amounts, we anticipate the prevention or amelioration of the disturbing and disabling concomitants of menstruation, chiefly irritation of nerves, as manifested most markedly in patients with epilepsy, and the irritation of smooth muscle which gives primary dysmenorrhea. The treatment of premenstrual tension is, on the whole, already satisfactory, but we are planning to try the protective pseudoglobulin in this disorder to test our idea that it is due for the most part to absorption of toxin. A crucial experiment would be the actual prevention of endometrial bleeding by the protective pseudoglobulin. In one patient, on two different occasions, the onset of flow appeared to be delayed by the injections when her period was due and she was having

molimina. Perhaps if injections were continued in sufficient amounts the endometrium would regress without desquamation. The results of such an experiment would undoubtedly yield definite information concerning the purpose of menstruation. On the basis of the laboratory work and the endocrine findings just before and during menstruation, we can think of one possibly justifiable purpose, namely, toxic stimulation of the hypophysis. Because of this we have postulated that the induction of postovulatory-like endometrial bleeding in patients with anovulatory disorders might, through the action of the toxin, result in better gonadotropic activity. This is perhaps one reason why the use of progesterone in larger and properly-timed amounts, with the ensuing menstrual-like bleeding, has been an advance in the treatment of anovulatory disorders. It seems significant also that patients given progesterone-induced flowing from a secretory endometrium often complain of uterine cramps.

From the facts already available, however, the menstrual toxin probably affects all the tissues of the body so that some broader purpose than just toxic stimulation of the hypophysis needs to be found. The menstrual phenomenon may reasonably be considered to fulfil the requirements of an "alarm" reaction and a "general adaptation syndrome"[3] and as such to keep the vegetative systems of the body "in line," as it were, for reproduction. This explanation still leaves unanswered why menstruation should be necessary in the female primate. We can only suggest that her vegetative systems would otherwise function improperly as a result of the increased cerebration presumed to occur because of her increased bulk of cerebral tissue.

II. The Termination of Normal Pregnancy

We have no positive evidence that a menstrual-like series of events plays any part in labor and delivery, but there are suggestive analogies between these episodes. Roughly, between the twenty-first and the second days before the onset of labor, when there is progressive withdrawal of the placental steroid hormones, retention of water takes place. Serum diastase decreases during the ten days before parturition, as it does before menstruation.[2] From studies thus far undertaken, Dr. Arthur T. Hertig has found evidence of retrogressive changes in the decidua in relation to delivery, for example, leucocytic infiltration. The circulating fibrinolysin and protective pseudoglobulin present after some hours of labor constitute another analogy to menstruation, although we are puzzled by the fact that these properties are not demonstrable at the start of spontaneous labor, especially since they appear in the circulation some hours before the onset of menstruation. We are likewise unable to explain by analogy why diuresis begins before labor, whereas it coincides with menstruation. We are, therefore, still hazy concerning the possible clinical significance of menstrual toxin in relation to the onset of labor, although the hormonal changes are entirely similar to those before and during menstruation and the development of toxemia of pregnancy, and in both of these situations there is good evidence of circulating toxin as a result of the withdrawal of hormonal support. The finding of circulating fibrinolysin and protective

TABLE I. PROTECTIVE PS TO PRE-ECLAMPTIC PATIENTS—EFFECT ON TOXIC SIGNS AND SERUM FIBRINOLYTIC ENZYME

PATIENT	BEFORE ℞ STARTED*			ADMINISTRATION OF PROTECTIVE PS.	RESULT		
	BLOOD PRESSURE AT 8 A.M.	ALBUMIN GRAMS IN 24°	FIBRINOLYTIC† ENZYME		BLOOD PRESSURE AT 8 A.M.	ALBUMIN GRAMS IN 24°	FIBRINOLYTIC† ENZYME
Mrs. J. K. aged 30 para I gr. II	150/100	1.9	C	2 × daily for 4 days	115/70	0.7	0
				then none for 6 days	150/90	1.8	C
Mrs. E. H. aged 25 para I gr. I	150/105	8.0	C	2 × daily for 4 days	120/85	3.2	0.5 (0 in spec. after i.v.)
Mrs. E. B. aged 22 para I gr. II	150/100	5.5	C	2 × daily for 6 days	128/85	2.1	0
				then none for 4 days	140/95	5.2	C
				then 2 × daily for 3 days	130/85	3.2	0.3
Mrs. F. L. aged 23 para I gr. I	120/85	2.0	0.8	2 × daily for 6 days	120/60	0.8	0.4
				then none for 5 days	140/100	2.9	C
				then 2 × daily for 2 days	120/80	1.3	0.6
Mrs. R. S. aged 23 para I gr. II	170/120	1.2	C	2 × daily for 6 days after 2 days	145/110	0.5	-
				after 6 days	210/130	4.0	C
Mrs. B. M. aged 25 para I gr. II	150/100	23.5	0.6	2 × daily for 6 days after 2 days	125/80	7.5	0
				after 6 days	150/105	12.5	0.4
				then 4 × daily for 1 day	150/90	8.0	0

*All patients (except in Case 6) had been on routine hospital toxemic regime for one to three weeks before treatment with PPs.

†Degree of dissolution of standard fibrin clot after incubation for twenty-four hours with euglobulin fraction of 5 c.c. of serum. C = complete. The figures represent the proportion of the total 1 c.c. volume dissolved at twenty-four hours.

pseudoglobulin after prolonged labor and following induced labor indicates that the toxin has been active. Furthermore, the well-known increased susceptibility of women at the time of delivery to shock from loss of blood and operative procedures and the occurrence of intra- and postpartum eclampsia are in keeping with the idea that a toxin is present. The occurrence of postpartum eclampsia would seem to point clearly to the decidua as its cause. We would theorize that the menstrual toxin does cause the prepartum retention of water and contribute to labor contractions through irritating the myometrium, but that something prevents fibrinolytic activity from manifesting itself in the circulation before and at the start of this event.

III. Toxemia of Pregnancy

O. W. Smith has described the finding of fibrinolysin and protective pseudoglobulin in patients with toxemia of pregnancy. A similarity to menstruation is also indicated by the following: the well-known retention of water, the withdrawal of estrogen and progesterone that precedes the disease, the decrease of serum diastase that preliminary studies[2] have shown to precede the disease, the increased uterine irritability, the systemic pathology which is like that of the premenstrual and early menstruating endometrium and, finally, the amelioration of the disease when the uterus is emptied and removal of decidua is under way. The fibrinolytic property of the blood of these patients disappears post partum. Therefore, we think that menstrual toxin is the precipitating cause of toxemia as well as menstruation. The presence of menstrual toxin in pre-eclampsia and eclampsia, however, remains to be proved, even though the circumstantial evidence for it is strong. Biological studies of the decidua, the blood coming away with the placenta and the lochial discharge remain to be performed. Whether or not the idea is new, we opine that toxemia of pregnancy is a disease peculiar to the human female because she menstruates, toxic separation of the placenta being the most striking example. Furthermore, we lean to the thought that once damage to systemic tissues by the menstrual toxin has progressed sufficiently, they themselves may release toxic protein and irreversibly aggravate the disease, making it similar to secondary or irreversible shock.

With the cooperation of the Boston Lying-in Hospital, O. W. Smith has thus far studied six patients with pre-eclampsia before, during, and after treatment with the protective pseudoglobulin made by her. The findings are shown in the accompanying table. All but the last patient had been in the hospital on toxemic regime for one to three weeks before the trial of therapy. In addition to the decreases of blood pressure and urinary protein and the disappearance or diminution of the circulating fibrinolysin, losses of one to five pounds in weight were effected. When treatment was omitted, the findings were reversed. When treatment was resumed the reductions again followed. Although the complete disappearance of urinary protein was not brought about with the limited amounts of pseudoglobulin available, 50 to 68 per cent decreases were achieved.

Although it could be argued that the drops in blood pressure resulted from injecting changed protein and that the decreases in albuminuria were attributable to reduced pressure, a number of observations are against this explanation. In the first place the quantitative tests during the control period showed increasing albuminuria prior to injections, despite the fact that in all the patients hypertension had been considerably reduced by routine clinical measures. Furthermore, the effect of injections upon albuminuria was very much more striking than upon the hypertension. Finally, if the results observed were merely due to administration of changed protein, it is unlikely that the observed losses in weight would have ensued, and even more unlikely that the fibrinolysin would have disappeared or become diminished. Because of this possibility, however, O. W. Smith treated one patient for one day with a preparation of pseudoglobulin which she had found to be inactive in protection tests. At the end of the twenty-four hour period, the patient's urinary albumin and blood pressure had risen and her serum still caused complete dissolution of a fibrin clot. Then an active preparation was used and the desired changes followed.

The results of these preliminary therapeutic trials seem to us best explained as effects of neutralizing a toxic protein by another protein derived from damaged tissues. That they were obtained with a protein shown to be protective against the menstrual toxin appears to confirm our hypothesis that menstrual toxin is the cause of toxemia of pregnancy. Considering the sources of the protective pseudoglobulin, however, and the evidence for the similarity of menstrual toxin and a protein of widely different origin, namely, canine necrosin, and the association of fibrinolytic activity with other conditions involving damage of tissues (and this is not a new observation, dissolution of incubated clotted blood having for years been noted in cases of severe sepsis, toxemia of pregnancy and shock from various causes), we feel that the significance of these clinical tests is broader, that toxic protein catabolites from damaged tissues in general and menstrual toxin may be identical* and that therapy with the sort of pseudoglobulin now under trial may have far-reaching possibilities. This feeling is consonant with the present increasing realization of the importance of protein in the maintenance of homeostasis.

References

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*Dierks,[4] for example, reported his studies of the endometrium and vaginal mucosa of a young woman dying of burns. The last menstrual period had begun fifteen days before death. Surface hyperemia and beginning coagulation necrosis characterized the late proliferative endometrium and the vaginal mucosa he interpreted as showing a picture typical of menstruation, namely, hyperemia and desquamation of the superficial layer.

LYMPHOPATHIA VENEREUM COMPLICATING LABOR

An Analysis of Thirty-Eight Cases

IRWIN H. KAISER, M.D., BALTIMORE, MD., AND
EDWARD L. KING, M.D., NEW ORLEANS, LA.
(From the Department of Obstetrics, Tulane University School of Medicine and Charity Hospital of Louisiana in New Orleans)

LYMPHOPATHIA venereum complicates pregnancy primarily by the inflammatory lesions it produces in the mother which impede the progress of labor. The dystocia produced by this disease falls into two anatomic groups. The first is caused by the elephantiasis-esthiomene variety of vulvar lesions. Its management in no wise differs from that of similar soft tissue outlet dystocia due to other causes. The second type is caused by the extensive scarring of the soft tissues of the pelvis, of which the rectum is usually the first involved. This is due primarily to the virus and also to the usually associated secondary infection. The problems presented by this second type are unique in obstetrics.

Information concerning this subject continues to accumulate. Nevertheless the latest editions of standard obstetric textbooks (Beck,[1] Greenhill,[2] Stander[3]) and the larger systems of obstetrics and gynecology (Adair,[4] Curtis,[5] Davis[6]) provide incomplete information if they mention the subject at all. The most recent general review of lymphopathia venereum similarly fails to discuss the obstetrical complications adequately.[28]

Only four series of cases of lymphopathia venereum complicating labor have been presented from American hospitals (Kassebohm and Schreiber,[7] Wilson and Hesseltine,[8] Kaiser,[9] and Finn[10]). Of these, but two provide adequate data on a large enough number of patients (Wilson and Hesseltine—18 patients; Kaiser—48 patients) to permit conclusions as to the conduct of labor.

It therefore seems appropriate to present a series of 38 labors in 28 women with pelvic lymphopathia venereum observed at the Charity Hospital in New Orleans between 1937 and 1946. Further, it is proposed to discuss this complication and the problems directly related to it on the basis of the material available in the literature.

Review of Literature

One hundred twenty-four instances of rectal stricture complicating labor appear in the literature. Seventy-eight of these are included in Kaiser's report to which the reader is referred. An additional 46 cases omitted from that report are summarized in Table I.

The first recorded case of rectal stricture complicating labor was presented by Dorsett[11] in 1920. His patient died of peritonitis due to a rupture of the rectum following forceps delivery. Sixteen years later Kassebohm and Schreiber[12] reported two more deaths, one of them due to rupture of the rec-

tum. In the same year Gaines and MacDowell[13] recorded still another fatality due to ruptured rectum. The first series was that of Kassebohm and Schreiber[7] in 1937, consisting of 18 patients including the two deaths earlier reported. Borde[14] in the same year published a monograph on the obstetric complications of lymphopathia venereum which included two postpartum deaths due to peritonitis (Cases 2a and 2b, Table I).

In 1938 Anderson[15] described a death due to ruptured uterus following version and extraction. Pollard and Hellendahl[16] in 1942 reported another fatality, due to ruptured rectum after breech delivery. In the same year Wilson and Hesseltine presented their series of 18 cases, including two cesarean sections, two patients with colostomy, and the first instance of delivery complicated by twins.

A series of 48 deliveries, including one death due to spontaneous intrapartum rupture of the uterus, was reported by Kaiser in 1943. He urged that cesarean section be reserved for those patients with extensive involvement of the pouch of Douglas or the pelvic soft parts. Spontaneous delivery and close postpartum observation were recommended in the event pelvic delivery was decided upon. In the same year Marcano[17] reported 14 cases from Venezuela, including three cesarean sections and one maternal death. The latter patient was delivered by version and extraction after unsuccessful attempts at forceps delivery. She went into shock immediately post partum and parenteral therapy was given. However, the pulse disappeared, the patient suffered "*trastornos nerviosos*" (convulsions ?) and expired in collapse. No autopsy is reported, but it seems likely that this patient died of hemorrhage due to a ruptured uterus. In 1944 Finn described 7 more cases, one of whom had a colostomy. Another of his patients suffered a ruptured uterus after four hours of labor and was successfully treated by section and hysterectomy. The maternal death recently referred to by Gusberg[26] has been previously reported by Pollard and Hellendahl.[16]

The first record of a patient delivered in the presence of a colostomy performed because of rectal stricture is that of Huet and Gauthier-Villars[18] in 1935 (later reported again by Vignes,[19] to whom Kaiser erroneously attributed this case). In 1942 Pollard and Hellendahl reported the first cesarean section done in the presence of a colostomy.

Reports of other isolated cases are included in Table I.

Experience at Charity Hospital

Thirty-eight deliveries productive of thirty-nine infants in twenty-six patients suffering from pelvic lymphopathia venereum have been found in the records of Charity Hospital in New Orleans for a period from 1937 to 1946. There were no maternal deaths. These cases are summarized in Table II.

At the time of delivery the parity of the patients was:

Para 0—6 cases
Para i —8 cases
Para ii —7 cases
Para iii—5 cases
Para iv—5 cases
Para v —3 cases
Para vi or more—4 cases

Nineteen patients, or 70 per cent of the group, have had but one delivery under our observation after the diagnosis of rectal stricture was established. Four patients have had two deliveries, two patients three, and one patient four deliveries. No individual is known to have had an exacerbation of the lymphopathia in association with pregnancy.

TABLE I. FORTY-SIX ADDITIONAL LABORS IN THE PRESENCE OF RECTAL STRICTURE RECORDED IN THE LITERATURE

AUTHOR	AGE	PARITY	DURATION OF LABOR	TYPE OF DELIVERY	FETAL WEIGHT	COMPLICATIONS
1. Dick, W.	?	?	?	Spontaneous?	?	
2. Borde, R. A.	29	?	20	Spontaneous	2,700	Discharge of pus from anus at full dilatation.
2a. *ibid.*	28	0	48	Forceps	2,760	Prolonged first stage. Maternal death in 24 hours due to peritonitis. Vagina, cervix and uterus intact. Incorrectly attributed to Vignes by Kaiser, Table I, Case 24.
2b. *ibid.*	32	0	?	Cesarean	4,230	Infant hydrocephalic. Maternal death due to peritonitis. Incorrectly attributed to Vignes by Kaiser, Table I, Case 23.
3. Anderson, H. E.	37	5	3½	Spontaneous	7-5	
4. Pollard et al.	?	?	?	Cesarean	?	Colostomy.
5. Rodriguez et al.	26	?	15	Spontaneous	2,100	Neonatal death.
6. Goldman, H.	30	?	–	Cesarean	7-3	
7. Wilson et al.	23	4	?	Cesarean	?	Pelvic mass.
8. Wilson et al.	26	2	?	Cesarean	?	Pelvic mass.
9. Wilson et al.	40	1	?	Forceps	?	Rectovaginal fistula.
10. Wilson et al.	32	1	?	Spontaneous	?	Twin delivery.
11. Wilson et al.	33	1	?	Spontaneous	?	Colostomy.
12. Wilson et al.	23	0	?	Spontaneous	?	} Same patient.
13. Wilson et al.	25	1	?	Spontaneous	?	
14. Wilson et al.	33	4	?	Spontaneous	?	} Same patient.
15. Wilson et al.	34	5	?	Spontaneous	?	
16. Wilson et al.	26	4	?	Spontaneous	?	
17. Wilson et al.	26	3	?	Spontaneous	?	
18. Wilson et al.	24	0	?	Spontaneous	?	
19. Wilson et al.	30	4	?	Spontaneous	?	
20. Wilson et al.	30	0	?	Spontaneous	?	Colostomy.
21. Wilson et al.	32	1	?	Spontaneous	?	Rectovaginal fistula.
22. Wilson et al.	32	2	?	Spontaneous	?	
23. Wilson et al.	37	1	?	Spontaneous	?	
24. Wilson et al.	?	2	?	Spontaneous	?	
25. Chavanne, F. C.	35	4	–	Cesarean	2,450	Rectovaginal fistula.
26. Marcano, M. O.	22	0	6	Cesarean	2,750	Pelvic scarring noted.
27. Marcano, M. O.	21	0	9	Cesarean	3,540	No cervical dilatation.
28. Marcano, M. O.	35	2	–	Cesarean	1,570	Rectovaginal fistula.
29. Marcano, M. O.	?	1	22½	Version and extraction	2,540	Maternal death in shock, following unsuccessful forceps, attempted because of fetal distress in second stage, and then successful version and extraction.
30. Marcano, M. O.	42	0	?	Forceps	2,900	Artificial anus. 400 Gm. twin delivered.
31. Marcano, M. O.	28	6	?	Forceps	3,500	Vaginal scarring
32. Marcano, M. O.	27	0	17	Spontaneous	2,180	Perineal fistulae.
33. Marcano, M. O.	?	0	10½	Spontaneous	3,030	Artificial anus.
34. Marcano, M. O.	25	3	5	Spontaneous	3,010	
35. Marcano, M. O.	24	0	20	Spontaneous	2,400	
36. Marcano, M. O.	?	4	11	Spontaneous	3,510	
37. Marcano, M. O.	42	11	4	Spontaneous	3,350	
38. Marcano, M. O.	28	3	5½	Spontaneous	3,450	Artificial anus.
39. Marcano, M. O.	30	1	17½	Spontaneous	3,270	Perineal and genital lesions present.
40. Finn, W.	?	4	?	Spontaneous	?	
41. Finn, W.	?	0	?	Spontaneous	?	
42. Finn, W.	?	2	6	Spontaneous	?	
43. Finn, W.	?	?	?	Forceps	?	Colostomy.
44. Finn, W.	?	?	?	Midforceps	?	
45. Finn, W.	?	0	?	Forceps	?	
46. Finn, W.	?	6	4	Cesarean	?	Rupture of lower uterine segment after one hour second stage. Hysterectomy.

Note: Fetal weight is given in pounds and ounces or grams as originally recorded by the author. "?" indicates that no information on this point is given in the original report. All presentations were by vertex.

TABLE II. THIRTY-EIGHT LABORS IN THE PRESENCE OF RECTAL STRICTURE OBSERVED AT CHARITY HOSPITAL

PATIENT	AGE	PARITY	DURATION OF LABOR (HOURS)	TYPE OF DELIVERY	FETAL WEIGHT	PUERPERIUM	COMPLICATIONS
1. L. T.	38	4–3–1–0–3	12½	Spontaneous	6–7	Afebrile	Colostomy
2a. S. O.	27	–0–	10	Forceps	5–10	Afebrile	Devine colostomy following a simple resection of rectum.
2b. S. O.	30	1–1–0–0–1	20	Forceps	6–3	Afebrile	
2c. S. O.	31	2–2–0–0–2	4	Forceps	7–9	Febrile	Permanent loop colostomy established since last delivery.
2d. S. O.	33	3–3–0–0–3	3	Spontaneous	3	Febrile	
3. I. G.	36	2–2–0–0–1	26	Cesarean	6–10	Febrile	Devine colostomy. Vertex failed to descend after full dilatation. Pelvic examination revealed extensive scarring in adnexal regions. Tubal ligation at section.
4. M. B.	36	2–2–0–0–2	16	Forceps	6–13	Afebrile	Abdomino-perineal resection and loop colostomy. Herniation of proximal loop two weeks from term responded to bed rest.
5. N. E.	35	1–1–0–0–1	--	Cesarean	5–9	Afebrile	Loop colostomy. Membranes ruptured prematurely and inductions of labor failed. Section followed by hysterectomy and bilateral salpingo-oophorectomy.
6. A. F.	35	5–0–1–4–0	18	Cesarean	?	Afebrile	Smith extraperitoneal operation done because of poor progress and prolonged ruptured membranes as well as presence of stricture of rectum.
7. C. B.	25	–0–	17	Forceps	4–11	Febrile	Marked scarring in pelvis noted. Second stage 6 hours.
8. O. T.	32	1–1–0–0–1	?	Forceps	?	Endometritis	Prolonged labor of 2 or 3 days duration with primary uterine inertia and intrapartum infection. Stillborn.

9a.	C. C.	30	8–6–2–0–6	5½	Breech extraction	7–7	Afebrile	
9b.	C. C.	31	9–7–2–0–7	8½	Spontaneous twins	4–8 4–12	Afebrile	
10a.	M. A.	27	–0–	55	Forceps	5–9	Afebrile	
10b.	M. A.	29	1–1–0–0–1	7	Spontaneous	7–2	Afebrile	Rectovaginal fistula. Presentation by right mentum anterior?
11.	M. B.	37	2–2–0–0–2	11	?	7–15	Afebrile	
12.	C. B.	31	1–1–0–0–1	3½	Forceps	6–7	One day fever	Cause of sepsis not determined.
13.	A. B.	35	1–1–0–0–1	16	Forceps	6–2	Afebrile	Rectovaginal fistula.
14.	V. B.	38	3–3–0–0–3	8	Spontaneous	7–5	Febrile	Cause of sepsis not determined.
15.	E. D.	29	–0–	12	Spontaneous	?	Febrile	Cause not determined. Stillborn premature.
16.	E. H.	29	–0–	31	Spontaneous	9	Febrile	Intrapartum infection. Stillborn.
17.	J. H.	23	2–2–0–0–2	9	Spontaneous	5–13	Afebrile	
18a.	A. H.	31	3–3–0–0–3	9	?	?	Afebrile	Premature macerated stillborn.
18b.	A. H.	33	4–3–1–0–3	5	Spontaneous	8–4	Afebrile	
18c.	A. H.	34	5–4–1–0–4	12	Spontaneous	7	Afebrile	
19a.	C. J.	22	1–0–1–0–1	7	Spontaneous	5–15	Afebrile	
19b.	C. J.	26	2–1–1–0–2	5	Spontaneous	6–4	Afebrile	
20.	H. P.	35	4–4–0–0–4	5½	Spontaneous	7–10	Afebrile	
21.	A. R.	22	–0–	10	Spontaneous	5–10	Afebrile	
22a.	C. S.	27	3–3–0–0–3	6	Spontaneous	4–14	Afebrile	Rectovaginal fistula.
22b.	C. S.	29	4–3–1–0–4	8½	Spontaneous	7–8	Afebrile	
22c.	C. S.	30	5–4–1–0–5	11½	Spontaneous	6–13	Afebrile	
23a.	C. S.	33	3–3–0–0–1	6½	Forceps	4–8	Febrile	Cause of sepsis not determined.
23b.	C. S.	37	4–3–1–0–2	4	Spontaneous	5	Afebrile	Rectal resection done since last delivery.
24a.	M. T.	32	7–4–3–0–4	?	Spontaneous	6–14	Febrile	Pyelitis.
24b.	M. T.	38	8–5–3–0–5	5	Spontaneous	?	Afebrile	
25.	O. W.	36	1–1–0–0–1	9	Spontaneous	6–15	Afebrile	
26.	C. W.	34	2–1–0–1–1	7	Spontaneous	6–9	Afebrile	

Note: Fetal weight is recorded in pounds and ounces. All presentations are by vertex unless otherwise noted. Each individual patient is assigned a number, and multiple deliveries in the same patient are designated by letter. ? indicates that no specific information on this point was found in the records.

Only two of the patients had contracted pelves, both of slight degree and of no clinical significance.

Five patients came to delivery, one of them on four occasions, with pre-existing colostomies. In two of these patients cesarean section was done. Three other patients had pre-existing rectovaginal fistulas, and another had had a rectal resection performed. There is little detailed information concerning the state of the strictures or the pelvic soft tissues. In many cases there were few spontaneous complaints referable to the bowels, and the rectal stricture was an incidental finding. Antepartum complications other than these were few in number.

At delivery thirty-two fetuses, or 82 per cent, were in normal vertex presentation and one was in breech. One presented by right mentum anterior. In five there is no record.

Method of delivery was as follows: spontaneously by vertex—twenty-three deliveries, or 59 per cent; forceps—ten, or 26 per cent; breech extraction—one; cesarean section—three, or 8 per cent; two not recorded. One twin delivery is included, both infants being delivered spontaneously by vertex.

Duration of total labor was not increased. There is no information available on the duration of the second stage of labor. Twenty-two labors, or 58 per cent, lasted under eleven hours, and seven more, or 18 per cent, lasted between twelve and eighteen hours. Only five labors lasted longer than eighteen hours. The most prolonged labor according to the records lasted fifty-five hours (Case 10a), but a review of the details makes it seem likely that about thirty-six hours of false labor are included in that figure. A secundipara (Case 8) suffered primary uterine inertia and intrapartum infection, but did well following forceps delivery. A grand multipara (Case 9) delivered a breech and twins without difficulty.

One patient (Case 2) delivered on four occasions in the presence of a colostomy, the latter two after a permanent loop colostomy had been established. The first three deliveries of term-sized infants were terminated by forceps, although labor in the last of these was of brief duration. Only the fourth delivery, a small premature weighing 3 pounds, terminated spontaneously. The mother recovered uneventfully each time.

Another patient (Case 3), a 36-year-old para 2-2-0-0-1* with a normal pelvis, was the most instructive one seen. She proceeded slowly but well in labor until full dilatation had been reached. Vaginal examination then disclosed membranes intact, vertex high, and cervix fully dilated. Extensive scar tissue involving the rectum, the rectovaginal septum, and all the soft tissues of the pelvis was palpated. The membranes were ruptured artificially, but despite good labor no further descent of the head occurred. Low cervical section and tubal ligation were carried out. At operation the rectum and lower sigmoid were found to be scarred, firm, and fixed to the sacrum. The entire posterior half of the soft tissues of the true pelvis were thickened and resistant, making clear that the failure of descent was due entirely to the infection of the soft tissues by lymphopathia venereum and its secondary effects. The patient had an uneventful convalescence. Had this patient been delivered by forceps or by version and extraction a tragedy would have been inevitable.

Two other cesarean sections were performed. A secundigravida (Case 5) failed to go into labor after premature rupture of the membranes despite several attempts at induction, and a section-hysterectomy was done. An essential primigravida (Case 6) also suffered premature rupture of the membranes and

*When parity is designated in this manner, the first number refers to the total number of pregnancies, the second to the full-term pregnancies, the third to premature deliveries, the fourth to abortions, and the last to the number of living children. In this example, the patient has been pregnant twice, had two full-term deliveries, no prematures, no abortions and one living child. She is a gravida iii, para ii.

made very poor progress when she finally fell into labor. In view of her age and the presence of the rectal stricture, an extraperitoneal section was performed. The results in these cases were excellent.

The puerperia in these thirty-eight deliveries were uneventful. Ten patients, or 26 per cent, had a febrile course, none of any gravity. There were no complications referable to the bowel complaints.

Two patients were sterilized, both at section.

The infants were not remarkable as to weight. Thirty-five, or 90 per cent, were living at birth. Two were stillborn following prolonged labors, and two more were stillborn prematures.

Discussion

There are now available for study 162 cases of labor in patients with rectal strictures and pelvic lymphopathia venereum. This study suggests certain rules for the conduct of labor in these patients, rules which have been previously discussed in part by several authors.

At this point a few comments on the incidence of this complication are in order. Finn[10] states that "lymphopathia venereum is an obstetrical rarity," and is echoed in the latest edition of Stander's textbook.[3] It is true that the disease is seen only rarely among white women in the United States, but it is not uncommon among Negro women. The series now reported from Harlem Hospital in New York,[7] the Johns Hopkins Hospital in Baltimore,[9] and the present series from New Orleans are sufficient to dispel any idea of actual rarity. Further, experience has shown that the incidence rises sharply when the members of the obstetric staff become interested in the complication, probably because under ordinary circumstances minor degrees of pelvic scarring are not likely to draw attention. From the data at hand it is not possible to make any reliable statement of the incidence of pelvic lymphopathia in gravidas. However, between 1937 and 1942, forty-two instances of this complication were seen at Charity and Hopkins Hospitals.

Since the finding of rectal stricture at once suggests the possibility of dystocia, we have summarized these 162 cases by mode of delivery in Table III.

TABLE III. MODE OF DELIVERY AND DEATHS IN 162 DELIVERIES IN THE PRESENCE OF PELVIC LYMPHOPATHIA VENEREUM

MODE OF DELIVERY	NUMBER	PER CENT	DEATHS		
			NUMBER	PER CENT OF 162 CASES	PER CENT OF CASES BY MODE OF DELIVERY
Spontaneous	104	64	2	1.2	2
Forceps	25	15	3	1.8	12
Cesarean section	20	12	1	0.6	5
Breech extraction	5	3	1	0.6	20
Version and extraction	4	3	3	1.8	75
Miscellaneous	4	3	0	–	–
Totals	162	100	10	6.1	

Of the 20 sections performed, the indications for the operation are noted in the reports of eighteen. Eleven of these sections were done because of dystocia, either anticipated or actual, due to pelvic scarring and rectal stric-

ture. Three other operations were performed for multiple indications, including the lymphopathic process in two instances. Lymphopathia venereum was therefore implicated in at least two-thirds of the sections done, and in a section rate of at least 8 per cent in the whole series. Its etiologic connection is questionable in Finn's patient, in whom the section was done for ruptured uterus. The other sections were done for hydrocephalus, contracted pelvis, failure of labor with prolonged rupture of the membranes, and failure of the cervix to dilate. Marcano has suggested that this last condition is due to infection of the cervix by lymphopathia with secondary scarring.

Forceps delivery preceded three of the maternal deaths, a mortality rate of 12 per cent for the procedures. Inasmuch as study of the individual cases makes it likely that several of the uneventful forceps operations were performed as elective prophylactic procedures, the mortality rate for indicated forceps is undoubtedly much higher.

Following breech delivery, done in five instances, there was one death due to rupture of the rectum. The infant's weight is not recorded in this case report, and we can speculate only as to the role of the aftercoming head in producing this accident.

Version and extraction was performed four times, once for placenta previa in a multipara with a slight stricture and a 2,250 Gm. infant, and three times for dystocia. All three of the latter patients died, one of a ruptured rectum, one of a ruptured uterus, and one in shock with her reproductive tract intact. This leaves no doubt that version is absolutely contraindicated in the presence of pelvic lymphopathia.

Spontaneous delivery occurred in 101 cases and eventuated in two deaths, one due to ruptured rectum, and the other due to ruptured uterus. Therefore, not even this form of delivery can be regarded as entirely free of risk.

The maternal mortality rate for these 162 cases is 6 per cent. In all likelihood this is exaggerated by the many reports which have been concerned with isolated fatalities. The six series of patients reported include 143 cases with four deaths, a maternal mortality rate of 2.8 per cent, which seems a more likely figure. It is noteworthy that antemortem diagnosis of rupture of the rectum has never been made in these cases. The results of treatment of rupture of the rectum due to trauma, consisting mainly of fluid replacement, chemotherapy, and colostomy to divert the fecal stream, are sufficiently good to warrant the hope that postpartum patients would respond well to such treatment. The diagnosis can be made on the basis of appearance of shock post partum, accompanied by severe lower abdominal pain. The signs of peritonitis appear within a few hours. In its early stages, the condition may be confused with rupture of the uterus which itself necessitates laparotomy. A preoperative differential diagnosis might be made by an x-ray taken in the lateral decubitus position for the demonstration of air in the peritoneal cavity, although it has not been attempted in these cases. The sine qua non of diagnosis is a high index of suspicion when the presence of pelvic lymphopathia in the parturient is known.

Review of the deaths discloses that five were due to rupture of the rectum, two to rupture of the uterus, and one to peritonitis following cesarean section for dystocia in the presence of intrapartum infection. In addition, three women died early post partum, and autopsy was not obtained. Two of these deaths appear to be due to rupture of the rectum (Kassebohm and Schreiber[12] and Borde[14]) and one to rupture of the uterus (Marcano.[17]) There is no striking correlation of death with age, fetal weight, or parity. In two of the fatal cases of ruptured uterus, dystocia due to lymphopathia played a role by occasioning version and extraction. In seven of the deaths there is a record of forceful obstetric intervention by operators who were evidently unaware of the risks they faced. The death from peritonitis following section in an infected patient might have been avoided by an extraperitoneal approach, or, at the present time, by intensive chemotherapy.

There remains no doubt that forceful delivery must be avoided in any patient with pelvic lymphopathia who shows evidence of dystocia. The clinical criteria to be employed in obstetric management must be based on the pathologic anatomy of the disease. In this regard we cannot agree with Eastman's[25] statement that:

> "Most important is the status of the rectovaginal septum. If this is involved in scar tissue, the elasticity of the vaginal wall is impaired, and tearing of the fibrosed vagina and attached rectum is likely."

Were this to occur, it should result in rectovaginal fistula or tears of the vagina, neither of which has been reported. In fact, the descent of the presenting part is impeded by scarring which is widespread in the pelvis. It is generally agreed that the virus of lymphopathia venereum spreads from the vulva by lymphatics to the perirectal lymph nodes and thence to the iliacs, leaving smouldering primary and secondary inflammatory changes in its wake. These produce the rectal stricture. In the patient with a severe or chronic case, the infection proceeds by retrograde spread in the bases of the broad ligaments and out laterally into the soft tissues of the pelvic wall. That labor is impeded by this cicatrized and unyielding mass was demonstrated classically in Case 3 of the series presented.

The rectum ruptures because its pelvic portion which is fixed to the vagina is torn away from the portion above the pouch of Douglas where it is adherent to the sacrum by scar tissue. The etiology of uterine rupture is not so clear. Two such ruptures followed version operations and were probably due to a combination of this procedure and the resistance offered by the soft tissues. Two uterine ruptures occurred spontaneously in multiparas and may simply have been coincidental. On the other hand, they may represent tearing of a lower uterine segment weakened by uterine contractions working against unyielding pelvic soft tissues.

The criteria for accouchement must be established with the condition of the soft tissues of the pelvis in mind. Presence of a rectal stricture will lead to further study of the patient, but it constitutes only a par of the anatomic picture. Examination is best performed under anesthesia. If, near term, the

soft tissues are so extensively involved as to preclude the passage of the presenting part, an elective section must be performed. The extent of the involvement may be judged in terms of fixation of the region of the pouch of Douglas, of adnexal thickening, and of the presence or absence of fistula formation. In most instances a trial of labor can be allowed, with the expectation that failure of descent of the presenting part will be followed by cesarean section rather than forceps or version, regardless of the state of dilatation of the cervix. Forceps should not be employed in patients with pelvic lymphopathia if the vertex is not at the outlet, unless failure to descend is exclusively due to some other obstetrical complication.

The presence of colostomy apparently does not present any special difficulties. One of our patients suffered a mild herniation of her colostomy about two weeks from term. This condition responded rapidly to bed rest and local care. Seventeen deliveries have been recorded in mothers with colostomies, without a maternal death, although presumably they suffered the most extensive disease of the group. It may be that diversion of the fecal stream allows resolution of some of the secondary infection and scarring. Three patients with colostomy delivered by section, seven by forceps, and seven spontaneously. For section, the area of the colostomy is simply draped out of the operating field. No wound infection due to contamination has occurred. Kaiser reported one colostomy and one precolostomy done at the time of section, with excellent results.

Postpartum care of patients with pelvic lymphopathia must be most meticulous for the first twenty-four hours, inasmuch as rupture of the uterus or rectum should be readily remediable if diagnosed. Heavy sedation should be avoided and the patient regularly and frequently examined. Peritoneal irritation or shock should immediately suggest rupture of the uterus or rectum, and indicate exploratory laparotomy.

Summary

Thirty-eight labors in the presence of pelvic lymphopathia venereum and rectal stricture observed in the Charity Hospital in New Orleans have been reported. There were no maternal deaths. Three cesarean sections were performed.

The 162 labors now recorded in the literature have a maternal mortality rate of 6 per cent, but this figure appears to exaggerate the actual risk. Force in delivery has played a large role in the reported fatalities. Version and extraction is absolutely contraindicated. Death is usually due to rupture of the rectum or uterus, either of which may occur with spontaneous delivery.

If soft tissue scarring due to lymphopathia venereum is widespread in the pelvis, the patient should be delivered by cesarean section. A trial of labor may be permitted, but if the presenting part fails to descend to the outlet, cesarean section rather than any form of pelvic delivery should be performed, regardless of the dilatation of the cervix. If the patient delivers per vaginam she should be watched diligently for signs and symptoms of rupture of the

uterus or rectum. The appearance of peritoneal irritation or shock should suggest exploratory laparotomy.

Colostomy presents no special obstetric problems other than those found in other patients with pelvic lymphopathia venereum.

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LYMPHOGRANULOMA VENEREUM IN OBSTETRICS

CHARLES M. STEER, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

LYMPHOGRANULOMA venereum is a virus disease which produces a small primary lesion and systemic manifestations in its early stages, and localizes its later stages in the genitals and lower bowel. Two distinct syndromes may be produced, and either of these may cause obstetric complications of the utmost gravity.

Incidence.—Lymphogranuloma venereum is a rare disease in general, and is even more rare in association with pregnancy. At the Presbyterian Hospital in New York the diagnosis of this disease was made in 126 cases over a period of fifteen years. With some 280,000 admissions during this time, a general incidence of 0.045 per cent is produced. On the Obstetrical Service (The Sloane Hospital for Women) there were eight cases among 22,500 admissions over the same period, an incidence of 0.036 per cent. These eight cases are included in the grand total of 126.

There were, in all, 75 women and 51 men; and the 75 women comprise the material of this study. In this group 68 patients were Negroes (including the eight obstetric patients) and seven white, a distribution which supports the impression that lymphogranuloma venereum is primarily a disease of the Negro race. The disease was associated with one or more of the other venereal diseases (syphilis, gonorrhea, and chancroid) in 39 of the 75 patients.

Relation to Fertility.—Whether lymphogranuloma venereum reduces the capacity of a woman to conceive and bear children is not clear at present. It has been demonstrated by Wilson and Hesseltine,[1] in a small group, that no impairment of the reproductive function is produced. The group reported in the present study demonstrates quite the opposite.

There were 45 patients in this group who became pregnant *before* the disease developed. The remaining 30 never became pregnant. No patient conceived for the first time *after* the disease appeared. Of the 45 women who became pregnant *before* the onset of the disease, only nine became pregnant again *after* the onset of the disease.

Among the 45 cases, 92 pregnancies occurring *before* the onset of the disease resulted in 62 living children, 3 stillbirths, and 27 abortions; while 17 pregnancies occurring *after* the onset of the disease resulted in 7 living children, 2 stillbirths, 8 spontaneous abortions, and one therapeutic abortion.

These figures suggest a definite impairment of fertility by the disease. In order to examine this possibility more closely, the influence of age was determined. There were 11 patients in the group which had borne children who

were 40 or more years of age at the time the diagnosis of lymphogranuloma venereum was made. When this group of 11 is excepted, there remain 34 cases potentially fertile at the time the disease appeared. Nine of these patients became pregnant again, with the results described above.

Relation to Obstetrics.—In the late stages, lymphogranuloma venereum causes two pathologic syndromes of obstetric significance. These are: (1) the ano-rectal syndrome, and (2) the genital syndrome or esthiomene.

In a space of five months, there appeared at the Sloane Hospital for Women three cases of the ano-rectal syndrome, each producing a different complication of the pregnancy. The first of these was a case of rupture of a rectal stricture which terminated fatally. This case, described in detail by Pollard and Hellendall,[2] may be summarized as follows:

J. T., 33 years of age, Negro, was admitted in labor at 2:40 A.M. on May 9, 1941. She had been treated as an outpatient for four years, and had a known rectal stricture. There was no proctitis. Her pelvis was gynecoid. The fetus presented as a breech, and shortly after admission the fetal heart became slow and irregular. A vaginal examination at this time disclosed a pulsating loop of cord prolapsed through a firm one-finger cervix. The patient was placed in Trendelenburg position, and the cord was replaced with much difficulty. Following this the fetal heart improved, and a No. 3 Voorhees bag was inserted. One hour later the fetal heart disappeared. She continued in labor for twelve hours, at the end of which time both feet and a loop of cord presented at the vulva. An easy breech extraction of a slightly macerated fetus was carried out.

The reaction to delivery was good, and one hour post partum she had a blood pressure of 100/78, pulse 88, temperature 100° F., and respirations 20. During the next eight hours there appeared increasing abdominal pain, tenderness, and distention. The pulse and respirations rose. The abdomen became stony hard; bloody fluid was passed by rectum; and twenty-one hours post partum the patient became suddenly comatose and died.

At autopsy there was found a complete tranverse rupture of the rectum, at a point 8 cm. above the anus. The ends of the rectum were 10 cm. apart. The lower 8 cm. of the rectum was markedly stenotic, with a lumen of 0.5 cm., and it was tightly bound down. The rupture occurred in the uppermost portion of this stricture. Above the rupture was a portion of normal colon 7 cm. long containing impacted feces, and above this was a second stricture 3.5 cm. long. There was marked generalized fibrinopurulent peritonitis.

There have been four similar cases previously described. In 1920 Dorsett[3] described a case of a 37-year-old patient who had had three previous deliveries without complications. She was delivered at home by low forceps. Almost immediately she had pain in the left side, very shortly went into shock, and died in forty-two hours. She had a known rectal stricture which was said to be syphilitic, the Frei test not having been described at that time. At autopsy there was found a rupture of the rectum at the rectosigmoid junction in the upper extremity of the stricture, and an acute diffuse peritonitis. In 1936 Gaines and McDowell[4] described the case of a 19-year-old white primipara with a history of "rectal trouble" for several years, who was seen for the first time in active labor for twenty hours. She had a very tight rectal stricture beginning just within the anus and extending as far as the finger could reach. Tucker-

McLane forceps were applied but delivery could not be effected. Version and extraction were then done, with episiotomy, and delivery was easy except for the head. This offered much difficulty, and was finally delivered very suddenly. The child was born alive. The patient went into partial shock, reacted once, and then died five and one-half hours after delivery. At post mortem there was a stricture of the entire rectum beginning 2 cm. above the anus. At a point 8.4 cm. above the anus was a laceration of the anterior and lateral aspect of the rectum opening directly into the peritoneal cavity. There was fecal fluid in the pelvic peritoneum and the pelvis. No Frei test had been done.

In 1937 Kassebohm and Schreiber reported 18 cases of rectal stricture in patients at term or in labor. Fifteen cases were delivered spontaneously with one death, a mortality of 6 per cent. Three operative deliveries occurred with one death, a mortality of 33 per cent. Autopsy on one of these deaths revealed a rupture of the rectum. In 1939 Vignes[6] reported a case of rectal stricture with positive Frei test in which there was narrowing of the superior portion of the vagina and elephantiasis of the labia majora. A labor of sixty-two hours was terminated by a forceps operation made very difficult by the induration of the vagina, and death occurred thirteen hours post partum with symptoms of peritonitis. No autopsy was done, but it was ascertained that there was no rupture of the uterus and no cervical laceration. The origin of the peritonitis was thought to be a rupture of the rectum.

In a second case seen at the Sloane Hospital, lymphogranuloma venereum with an acute flare-up of the disease in the sigmoid and rectum constituted the complication to pregnancy:

E. H., a 36-year-old Negro multipara, was admitted to the Antepartum Clinic in May of 1941, at which time she was two months pregnant. She had had a known rectal stricture and proctitis for six years, with no change under treatment. In November, 1938, a cesarean section had been done at the Sloane Hospital for Women because of the stricture. At the time she appeared in this next pregnancy (May, 1941), termination of the pregnancy was advised but the patient refused it. She remained relatively well for three months, but on Aug. 31, 1941, she was seized with sudden lower abdominal pain, diarrhea, distention, vomiting, and a fever of 103° F. The pain localized to the left lower quadrant, and the diarrhea produced as much as 4 liters of foul feces per day. The colon became enormously dilated and the uterus was pushed to the right. There was no improvement with sulfaguanidine. Opiates gave partial relief. On the eleventh day of the acute episode she passed feces per vaginam with some decrease in pain and distention. On the eighteenth day she began to pass increasing amounts of pus by rectum, and a steady improvement in her general condition began. The fever disappeared during the next month. On November 30, she went into labor one month before her expected date of delivery. A cesarean section and hysterectomy were done, and a small but otherwise normal child of 1,950 Gm. was obtained. The postoperative course was uneventful.

The third was a patient with a long-standing stricture who developed complete intestinal obstruction during pregnancy:

M. P., a Negro para iv, gravida v had had a perirectal abscess at the age of 10 years. At 18 years of age, when pregnant for the first time, she had repeated perirectal abscesses and fistulas, and a diagnosis of rectal stricture was made. The Wassermann was four plus. A normal spontaneous delivery fol-

lowed, and there was a second at 20 years of age. At 22 years, with proctitis continuing, delivery at term was obstructed by a circular band of scar tissue beneath the vaginal mucosa just within the introitus. This band gave way during a midforceps delivery, but the mucosa remained intact. The next year the rectal stricture was divided but it recurred. At 24 years another normal delivery occurred. In the next 8 years there were continuing proctitis and intermittent inguinal swellings, together with occasional systemic symptoms.

In 1941, at 32 years of age, she became pregnant again. Constipation, lower abdominal pain, and proctitis increased until at seventeen weeks gestation complete intestinal obstruction developed. This was only partially relieved by a Miller-Abbott tube and colon lavages, and at eighteen weeks the pregnancy was terminated by supravaginal hysterectomy. The postoperative course, with tube in place for six days and then without tube, was remarkably free of distention. Two months later she felt quite well and was having daily bowel movements without pus or blood, although the stricture was quite narrow.

Esthiomene

The late syndrome of esthiomene or elephantiasis has also produced a number of cases of dystocia. Cohen, in 1930,[6] reported a case of ulceration of the vulva with elephantiasis which caused great difficulty in extracting the aftercoming head. He quotes a case of Tschnewski in which perforation of the aftercoming head was necessary under similar circumstances. Riviers and Boursier[6] had to resort to cesarean section after a trial of labor in a case of marked elephantiasis of the labia minora and clitoris in which the vaginal introitus was constricted and indurated, especially over the perineum. Delivery was done by cesarean section after a trial of labor had been given.

Delivery From Below

Labor is not always obstructed and complications are not the invariable rule in cases of lymphogranuloma venereum. At the Sloane Hospital there have been four full-term deliveries and one premature normal delivery in cases of rectal stricture. Of the 18 cases reported by Kassebohm and Schreiber, 15 patients were delivered spontaneously and three operatively. In the 16 cases which survived, the morbidity was 50 per cent, but there were no other complications. Wilson and Hesseltine reported 18 patients with a total of 58 pregnancies, 21 of which were observed. These resulted in 19 living children and 3 abortions (two therapeutic). The deliveries were carried out by cesarean section in two cases, once for extensive sloughing of the vagina and once for a large pelvic mass. One patient was delivered uneventfully by low forceps, and the remaining 16 had nonoperative deliveries. Two of these had permanent colostomies because of severe strictures. A third, a case of twins had a fecal impaction above a stricture. The stricture was dilated during labor and the impaction removed by repeated enemas, after which engagement and delivery occurred. Huet and Gauthier-Villars[6] had a case of severe proctitis due to lymphogranuloma which required a colostomy. Two normal deliveries occurred despite continuing disease which completely obliterated the rectum. Anderson[8] reported a patient with marked proctitis and large stricture, together with elephantiasis of the labia majora. This patient had three quick normal deliveries despite the stricture. Michelson[9] and Dick[10] each had a case of stricture with a normal delivery.

Discussion

The described cases, and those reported in the literature, demonstrate that lymphogranuloma venereum which has progressed to its late stages produces a serious complication in the pregnant patient. It would further appear that, in this series, the presence of the disease also diminishes the fertility of the patient.

When conception does occur in a patient with rectal or genital involvement, there may result a normal pregnancy and a spontaneous delivery. But in other cases, and it is impossible to predict which ones these will be, there may occur a flare-up of the disease during the pregnancy, or the rectal involvement may proceed to the point of complete intestinal obstruction. Because of these possibilities, it would seem wise to advise against pregnancy in a patient with active disease or with a rectal stricture, and termination should be considered if pregnancy has occurred in such a patient.

The chief danger which exists at the time of delivery is that of rupture of the rectum. In the reported cases this has always resulted in death, and this accident has been associated with an operative procedure in all but one case. This means that vaginal delivery of a patient with a rectal stricture exposes her to the possibility of irreparable damage. It is true that a number of patients have been delivered uneventfully from below, and this number is greater than the number of those who have died. But with the risk so great, it would seem wiser to deliver all patients with rectal strictures or the genital syndrome by cesarean section. Where this cannot be done, the delivery may be allowed to take place from below if operative interference is kept to a minimum, and when interference cannot be avoided the manipulations should be as gentle as possible.

Summary

1. The incidence of lymphogranuloma venereum has been recorded, with particular reference to obstetrics.

2. Impairment of fertility by the disease has been demonstrated.

3. The gravity of the possible complications warrants advising against pregnancy in a patient with active disease or a rectal stricture, and warrants consideration of termination if pregnancy has occurred.

4. In patients with rectal stricture or esthiomene the method of choice for delivery is by cesarean section.

5. If delivery must be allowed to take place from below, manipulation should be carried out only when it is unavoidable.

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DOES RH-ISOIMMUNIZATION CAUSE EARLY ABORTION?*†

E. W. Overstreet, M.D., H. F. Traut, M.D., Marjorie Hunt, M.A., and S. P. Lucia, M.D., San Francisco, Calif.

(From the Division of Gynecology and Obstetrics and the Sub-Division of Preventive Medicine, University of California Medical School)

In 1942 Levine[1] suggested that maternal isoimmunization by fetal Rh antigen might play an etiologic role in spontaneous early abortion. He stated that "clinically it was already known that mothers of erythroblastotic infants have a higher than normal incidence of spontaneous abortion," and he illustrated this statement by presenting the outcomes of 37 pregnancies in 7 Rh-negative mothers, 6 of whom showed anti-Rh serum agglutinins. Ten of these pregnancies aborted, giving an abortion rate of 27 per cent—considerably higher than normal expectation.

Since Levine's report, and coincident with the recent intensified interest in the role of Rh-isoimmunization in pregnancy, it has been generally assumed that a considerable number of early abortions could be attributed to this mechanism. Many authors,[2-6] in discussing either the over-all problem of abortion or the clinical aspects of the Rh factor in pregnancy, have emphasized a supposed responsibility of the obstetrician in this regard. They have urged that cases of habitual abortion or even patients who have simply aborted a single pregnancy be subjected to immediate study of the Rh status of both marital partners in the hope of accounting for the abortion tendency.

Yet the medical literature offers no study which demonstrates conclusively that Rh-isoimmunization plays any part in causing early abortion. Indeed, some evidence to the contrary is available. Javert,[7] from a study of 55 cases of erythroblastosis and 12 cases of habitual abortion, concluded that "unless additional evidence shows the contrary, early habitual abortions should not be attributed to isoimmunization." Hunt[8] studied 25 cases of habitual abortion with reference to the Rh factor and concluded that "the Rh factor is not of great importance as a common cause of such untoward terminations of pregnancy."

In spite of such findings the opinion persists, even in the very recent literature, that Rh-isoimmunization probably plays a part in the causation of a certain number of early abortions—if not in the so-called habitual abortions, then at least in single or spaced abortions of Rh-negative mothers with Rh-positive husbands. It is our hope that the statistical evidence here presented may cast further light on this belief.

Clinical Material

An analysis is made of 1,038 pregnancies occurring in 226 Rh-negative mothers from the Division of Obstetrics and Gynecology of the University of

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California Hospital and 286 Rh-negative private patients from the private practice of one of the staff members of that hospital.* The control series consists of 1,129 pregnancies occurring in 237 Rh-positive mothers from the same clinic and 297 Rh-positive mothers from the same private practice. All the Rh-negative patients obtainable from both sources were used, and a comparable number of Rh-positive patients were selected from both sources by a purely alphabetical random choice. Exclusion of patients from the series was done only on the basis of incompleteness of data. Cases included were studied from 1944 to the present.

Inasmuch as data on the Rh status of husbands were incomplete, Rh-negative mothers with Rh-negative husbands have been included in the series. The number of cases is great enough, however, so that we may safely assume for the Rh-negative group of mothers approximately an 85 per cent incidence of "Rh-incompatible" matings. Data on the Rh status of the delivered infants were, for various reasons, equally incomplete, so no attempt is made to present them.

Rh determinations on all patients were carried out in the laboratory of the Sub-Division of Preventive Medicine of the University of California Medical School. The patient's own statement regarding the outcomes of previous pregnancies was accepted whenever it was deemed reasonably dependable. If there was doubt whether an early termination of pregnancy represented an abortion or premature delivery of a viable infant, that pregnancy was excluded from the series. ("Viable" is here used in the sense of duration of pregnancy greater than five lunar months.) Any error present in the series on this account is equally present in the control series.

A certain degree of error arises, however, from the tendency of many patients to conceal a history of previous induced abortion, such a termination of pregnancy often being reported as a spontaneous one. For this reason no attempt has been made in this series to separate spontaneous from induced abortions. Indeed, the "abortion rate" quoted in the tables represents *all* interruptions of pregnancy prior to the fifth lunar month. The incidence of mole, therapeutic abortion, and the like, is extremely small, however; and here again the equal and large sizes of the two series makes it possible to draw valid conclusions from a comparison of them.

Material is also presented to arrive at the abortion rate in the pregnancies of mothers who at any time during their childbearing careers bore an infant which manifested hemolytic disease of the newborn. The criteria used for the diagnosis of this condition are those previously discussed by Overstreet and coworkers.[9] They have been adhered to in both the private and the clinic series of cases. Since the latter two series are essentially identical in size, handling of patients, criteria for diagnosis, number of patients, and serological study, their analytical treatment as a single series is justified and leads to more mathematically significant conclusions. It may be added in passing that a separate statistical analysis of the private and clinic cases shows only an increased sampling error with no findings at variance with those of both series treated as a unit.

Findings

Table I presents the total abortion rate for 1,129 pregnancies in Rh-positive mothers, 15.2 per cent, as compared with that of 1,038 pregnancies in Rh-negative mothers, 12.4 per cent. The difference in rate, *opposite* to what one would expect if Rh-isoimmunization played a part in causing early abortion, is explainable only on the basis of sampling error.

Table I also presents the abortion rate for primigravid pregnancies and for multigravid pregnancies in the Rh-negative and the control series. It has

*We are greatly indebted to Dr. Ernest W. Page for the opportunity to include in this analysis the data obtained from private patients.

been amply demonstrated that Rh-isoimmunization and the fetal damage it produces become more manifest in succeeding pregnancies. We should expect, then, that isoimmunization, if it played a part in early abortion, would produce in

TABLE I. ABORTION RATE IN RH-POSITIVE AND RH-NEGATIVE MOTHERS

TYPE OF PREGNANCY	MOTHERS' Rh STATUS	ABORTION RATE
All pregnancies (2167)	Rh-positive (1129)	15.2% (171)
	Rh-negative (1038)	12.4% (129)
Primigravid pregnancies (1046)	Rh-positive (534)	12.2% (65)
	Rh-negative (512)	10.9% (56)
Multigravid pregnancies (1121)	Rh-positive (595)	17.8% (106)
	Rh-negative (526)	13.9% (73)

multigravid pregnancies an abortion rate appreciably higher than that for the Rh-positive, multigravid controls. No evidence of this is manifest in our series. While the abortion rate rose from 12.2 per cent in the primigravid pregnancies of Rh-positive mothers to 17.8 per cent in the multigravid pregnancies of Rh-positive mothers, it rose only from 10.9 per cent in the primigravid pregnancies of Rh-negative mothers to 13.9 per cent in the multigravid pregnancies of Rh-negative mothers. Were it not for the fact that this difference in increase is certainly due to sampling error, one might even say that Rh negativity conferred a small degree of protection upon the multigravid pregnancies of Rh-negative mothers so far as abortion is concerned. There is, at any rate, no evidence that Rh-negativity contributes to the abortion rate of multigravid pregnancies any more than it does to that of primigravid pregnancies.

It is, however, in the pregnancies of the Rh-negative mother who has fully demonstrated her ability to form damaging antibodies—by bearing a child manifesting hemolytic disease—that we might expect to find the highest abortion rate of all. Whether it would appear in the primigravid pregnancies of such mothers is doubtful, but we surely might expect the multigravid pregnancies of a mother who had had one or more erythroblastotic infants to be subject to a high incidence of early interruption due to Rh-isoimmunization. The pregnancies of 45 such mothers are presented in Table II.

TABLE II. ABORTION RATE IN RH-NEGATIVE MOTHERS WHO HAVE BORNE AT LEAST ONE CHILD WITH HEMOLYTIC DISEASE OF THE NEWBORN

TYPE OF PREGNANCY	MOTHERS' Rh STATUS	ABORTION RATE
All pregnancies	Rh-positive (1129)	15.2% (171)
	Rh-negative (135)	14.1% (19)
Primigravid pregnancies	Rh-positive (534)	12.2%
	Rh-negative (45)	6.7% (65) (3)
Multigravid pregnancies	Rh-positive (595)	17.8% (106)
	Rh-negative (90)	17.8% (16)

Both the over-all abortion rate, 14.1 per cent, and the rate for multigravid pregnancies, 17.8 per cent, are no higher than they are for the corresponding pregnancies in Rh-positive mothers, 15.2 per cent and 17.8 per cent, respectively. The extremely low rate for primigravid pregnancies of Rh-negative mothers is doubtless due to the small number of pregnancies and consequent large sampling error. In any event, in none of the pregnancies of this special group of Rh-negative mothers is the abortion rate apparently contributed to by the known capacity of their mothers for Rh antibody production.

Perhaps a more concrete approach to the question may be undertaken through an examination of the salvage of viable infants from the pregnancies of Rh-positive mothers, Rh-negative mothers, and Rh-negative mothers who have

TABLE III. RECOVERY OF VIABLE INFANTS FROM RH-NEGATIVE MOTHERS

FROM NUMBER OF PREGNANCIES	WHICH WERE	TYPE OF PREGNANCY	WERE OBTAINED	NUMBER OF VIABLE INFANTS
534	Primigravid,	Rh+ mother		469
512	Primigravid,	Rh+ mother	$(\frac{512}{534} \times 469 =)$	450
512	Primigravid,	Rh- mother		456
595	Multigravid,	Rh+ mother		489
526	Multigravid,	Rh+ mother	$(\frac{526}{595} \times 489 =)$	434
526	Multigravid,	Rh- mother		453

TABLE IV. RECOVERY OF VIABLE INFANTS FROM RH-NEGATIVE MOTHERS WHO HAVE BORNE AT LEAST ONE CHILD WITH HEMOLYTIC DISEASE OF THE NEWBORN

FROM NUMBER OF PREGNANCIES	WHICH WERE	TYPE OF PREGNANCY	WERE OBTAINED	NUMBER OF VIABLE INFANTS
45	Primigravid,	Rh+ mother	$(\frac{45}{534} \times 469 =)$	40
45	Primigravid,	Rh- mother		42
90	Multigravid,	Rh+ mother	$(\frac{90}{595} \times 489 =)$	74
90	Multigravid,	Rh- mother		74

borne erythroblastotic infants. These data are presented in Table III and Table IV. The expected salvage for a given number of Rh-negative mothers is simply calculated from the actual salvage obtained from the whole Rh-positive control series. It will be noted that in each instance the recovery of viable infants from the pregnancies of Rh-negative mothers was equal to or greater than the recovery from an equal number of pregnancies of Rh-positive mothers. We are, therefore, unable to adduce any statistical evidence that Rh-isoimmunization cuts down, by means of abortion, the number of viable infants one would expect to recover from a given number of pregnancies.

Discussion

Our general knowledge of the mechanism of Rh-isoimmunization in pregnancy has now become extensive enough so that we may, with some profit, consider theoretically its possibility as an etiologic factor in early abortion. Voluminous work has established the fact that fetal damage by Rh-isoimmunization does not occur in the absence of maternal production of Rh antibodies, either

anti-Rh or blocking. Moreover, Page, Hunt, and Lucia[10] have recently shown that maternal antibodies must be produced for a certain *period of time* before clinically appreciable fetal damage occurs. They have determined this period to be approximately ten weeks.

One must distinguish, of course, between fetal damage and placental damage. While it is possible that placental damage taking place earlier than fetal damage might account for early abortion due to Rh-isoimmunization, all our present knowledge indicates that such placental damage takes place concurrently with or somewhat later than fetal damage. Many cases of subclinical hemolytic disease of the newborn, for example, appear to have normal placentae so far as routine microscopic examination of placental sections is concerned.

It seems likely, therefore, that at least ten weeks of maternal sensitization must take place before the mechanism can play any part in the termination of pregnancy.

Our present knowledge does not include the stage of fetal development at which fetal red blood cells first show the presence of Rh antigen. Bornstein and Israel[11] were able to demonstrate its presence in the red cells of a non-macerated fetus 17 cm. in length, that is, at approximately four months duration of pregnancy. Earlier development of the anitgen is likely, but specific evidence is lacking. While reasoning by analogy is dangerous, it should be pointed out that Kemp[12] was able to demonstrate only the probable presence of B agglutinogen in a fetus thirty-seven days old, and at this age the agglutinogen strength was very low. Should essentially the same be true of the Rh antigen, it may well be that the first two to four weeks of pregnancy are incapable of producing any isoimmunization.

If we may further assume—as would seem permissible from the data of Page, Hunt, and Lucia—that several weeks more than the ten-week period might be required to produce damage extensive enough to result in expulsion of the pregnancy, then the summation of the time factors alone would be in the neighborhood of twenty weeks, the onset of the period of viability.

The foregoing discussion is in no sense an attempt at theoretical disproof of the Rh-isoimmunization etiology of early abortion. It is simply offered as a possible explanation for the absence, in our series, of any statistical evidence for the existence of such an etiologic factor.

Moreover, now that serologic studies on the Rh factor in pregnancy have been carried out for a number of years, many of us have encountered individual cases whose circumstances argue strongly against Rh-isoimmunization as an abortifacient mechanism. The following patient is a case in point.

Mrs. V. L. is a 41-year-old gravida vi, para 0, with a negative Kahn and Kolmer whose last menstrual period began on July 8, 1946. There is no history of transfusion. The husband is Rh-positive. The first pregnancy, 1928, terminated in spontaneous birth of a 7-pound infant who received transfusion but died in twenty-four hours. The second pregnancy, 1930, terminated in a full-term stillbirth, cause unknown. The third pregnancy, 1933, terminated in a

stillbirth at eight months, with marked edema of the child. The fourth pregnancy, 1936, terminated in a stillbirth at seven months, with marked edema of the child. The fifth pregnancy, 1938, terminated in a stillbirth at six months, cause unknown.

One week before the last menstrual period associated with the present pregnancy the patient's blood showed a 1+ anti-Rh titer with partial blocking. Next titer taken in twelfth week of pregnancy showed 4+ anti-Rh. All subsequent titers have shown between 2+ and 4+ anti-Rh with partial blocking on two occasions. The patient at present is in the thirty-second week of pregnancy.

Here we have a patient who has had repeated loss of infants due to Rh-isoimmunization—five pregnancies with no living child. Yet all her pregnancies have reached a viable size. In the face of repeated maternal sensitization sufficient to produce premature delivery and stillbirth due to erythroblastosis no pregnancy has been spontaneously aborted. The maternal blood showed a 1+ anti-Rh titer even before the onset of pregnancy and a 4+ titer early in its course, yet the pregnancy is now in its thirty-second week and the patient has at no time presented any symptoms of threatening abortion. If Rh-isoimmunization played any role in the causation of abortion, it is almost inconceivable that this patient should not have aborted at least one of her pregnancies.

Summary and Conclusions

1. A statistical analysis of the outcomes of 1,038 pregnancies of 512 Rh-negative mothers as compared with those of 1,129 pregnancies of 534 Rh-positive mothers is presented. The abortion rates for all pregnancies of Rh-negative mothers, for primigravid or multigravid pregnancies of Rh-negative mothers, and for pregnancies of Rh-negative mothers who have borne at least one child manifesting hemolytic disease of the newborn are no higher than for the corresponding pregnancies of Rh-positive mothers. The salvage of viable infants from the pregnancies of Rh-negative mothers is equal to or slightly greater than that from the corresponding pregnancies of Rh-positive mothers.

2. Doubt is cast upon the assumption that Rh-isoimmunization is an etiologic factor in early abortion.

3. A theoretical explanation is offered to account for the findings.

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Addenda

The subsequent course of this patient—after acceptance of this paper for publication—is of especial interest. It was determined that the sixth and present pregnancy was sired by a second husband, also Rh positive, while the first five had the first husband as father. The patient delivered spontaneously, three days past the estimated date of confinement, a living, Rh-positive, 3,080 Gm. child who manifested mild hemolytic disease of the newborn and required two transfusions. Postpartum serologic study of the maternal and fetal blood suggests, but does not prove, that isoimmunization during the sixth pregnancy was produced by an antigen of a different Rh subgroup than that responsible in the first five pregnancies. From the point of view of isoimmunization, then, the sixth pregnancy might correspond to a primigravid one.

Since submission of this material for publication, a paper by Hunt[13] has presented a similar study of the incidence of abortion in 333 pregnancies of Rh-negative mothers. We are happy to add further statistical support to his conclusion that "casual or ordinary abortion seems uninfluenced by the mechanism of the Rh factor."

STUDIES IN UTEROTUBAL INSUFFLATION*

HERBERT F. NEWMAN, M.D., NEW YORK, N. Y.
(From the Gynecological Service and Laboratory, Beth Israel Hospital)

TRANSUTERINE insufflation of gas holds an established place as a clinical means of determining tubal patency in cases of human sterility. The application of kymographic recording methods to insufflation of both human beings and experimental animals has suggested many hypotheses of both academic and clinical import. Many of the conflicting deductions which have been advanced in the past are due to lack of suitable research instrumentation. This investigation was undertaken to determine the clinical value of uterotubal insufflation from two aspects:

1. Technique of insufflation and criteria of patency;
2. Significance and value of the kymographic tracing.

Determination of Patency by Insufflation

The physical principle behind the employment of insufflation for the determination of tubal patency is that the pressure in a gas-filled system depends upon the differential between the rate of gas inflow and the rate of gas escape. For clinical purposes, the ideal instrument should be one that can deliver the minimum quantity of a nontoxic gas at a constant, measurable slow rate of flow with a suitable manometer registering the pressure developed in the system.

Believing that manometric determinations alone are sufficient to indicate clinical patency, I do not await the confirmatory evidence gained by the introduction of 10 to 15 c.c. of gas, which is the minimum required to induce "shoulder pain" or be visible as a subphrenic collection to x-ray. Satisfactory determinations can be secured by the intraperitoneal insufflation of but 2 to 3 c.c. of gas. When such small amounts are used, the choice of gas becomes relatively unimportant. Carbon dioxide is employed largely for its theoretical advantages of low toxicity, high solubility, and easy procurement. Inert poorly soluble gases would probably produce less experimental error, and the danger of symptomatic air embolism becomes highly remote when small quantities are insufflated. Five cubic centimeters of atmospheric air have been frequently injected intravenously into rabbits without inducing convulsions or death, whereas the introduction of larger amounts is a common technique of sacrificing the animal. Although detailed protocols on all embolic case fatalities following clinical insufflation are not available, it is probable that considerably much more than 5 c.c. of gas under pressure was introduced.

To meter the gas at a slow, measureable rate, Rubin's volumeter was replaced by a rotameter. The objections to the volumeter are manifold:

*This investigation was enabled by a grant furnished by the J. M. Kaplan Fund.

1. This device does not directly indicate flow rate at any particular instant. Operating on a siphon principle, wherein gas displaces water so that 25 to 40 c.c. of gas are delivered with each regurgitation, calibration is necessary prior to each test. This is time consuming and wasteful of gas. Introducing a shut-off valve distal to a fixed setting of the flow-regulating valve does not furnish an accurate solution because of the fluctuation in delivery of the best needle valves.

2. The gas enters the uterus after having been moistened by the unsterile water in the volumeter.

3. Evaporation of water from the volumeter requires frequent refilling. The rotameter consists of a small glass tube with a tapering lumen through which the passing gas floats an aluminum marker. This gauge is calibrated to produce a linear relation between the height of the marker and rate of gas flow.

For the gas to flow, it must enter the system at a head of pressure exceeding a working range of five pounds. A tank of gas under greater pressure will ensure flow, but the rate of flow cannot be kept truly constant. With a tank pressure of twenty pounds, a variation in flow of the order of twenty per cent may occur between rate of delivery of gas at atmospheric pressure and one against a resistance of 200 mm. Hg. This error can be reduced by admitting gas at a pressure higher than twenty pounds, but it has not been possible to secure adequate rotameter calibration or fine enough needle valves which would operate at high pressures. In the Rubin apparatus, the flow-controlling needle valve is proximal to the volumeter. To overcome this unmeasured resistance, the valve has been placed distal to the rotameter.

To record the pressure in the system, an aneroid or mercury manometer may be used. The former has the advantage of compactness and it requires less gas to produce a reading comparable to that secured by the mercury manometer.

The uterus is sounded to determine the direction of the canal and to rule out a stenosis of the cervix. A Keyes-Ullman cannula is introduced and, in most cases, satisfactory leak-proof obturation may be secured without counter-traction on the cervix with a tenaculum. For cases with markedly dilated cervical canals, the screw type of cannula is preferable.

The gas is introduced at a rate of 10 c.c. per minute, a rate much slower than the 60 c.c. recommended by Rubin. There are two factors serving to limit the rate of gas flow. At a minimum, it must exceed the rate of gas absorption through the intact uterine mucosa. In several cases with known tubal obstruction, carbon-dioxide was introduced to build up a pressure of 200 mm. Hg., and the time for absorption of the measured quantity of gas was determined. Absorption is at a rate slower than 0.1 c.c. per minute. The maximum rate of flow is conditioned by the rate at which the operator wishes the pressure to rise in the system. Gas frequently fails to pass through the tubes at pressures of 200 mm. Hg. at a rate of flow of 60 c.c./minute when it has entered at lower pressure levels when the rate of flow was reduced. The explanation for this phenomenon is not clear, but the rapid distention of the uterus at higher rates of flow may conceivably produce "reflex spasm" of a functional nature.

Rubin has introduced manometric criteria for patency based upon numerous human insufflations.[1] With normal patency, he estimated that 120 mm. Hg is the upper limit of pressure developed when rates of gas flow are of the order of sixty cubic centimeters per minute. At slower rates of flow, this manometric limit should be lower and is probably of the order of 80 to 100 mm. Hg. However, thousands of insufflations must be performed on normal, fertile women to learn, statistically, this true upper limit of pressure compatible with functional patency. Mere escape of gas into the peritoneal cavity does not imply that the

tubes are patent enough for the passage of a fertilized ovum. The diameter of the ovum at its discharge from the follicle is approximately 100 to 150 micra. If the outlet of the apparatus is reduced to this diameter, a flow rate of ten cubic centimeters of gas per minute develops no pressure within the system whereas at sixty centimeters per minute, a flat level of 10 mm. Hg of pressure is generated. Of course, these mechanical observations cannot be directly applied to consideration of transit of a fertilized ovum, but when the subject of mechanical stenosis is considered it presents us with the order of lumen diameters secured at particular pressures. With adequate control of physical factors in the apparatus and increasing experience in insufflation to detect leakage of gas at the cervix, it is possible to eliminate the confirmatory evidence of "shoulder pain" or pneumoperitoneum to x-ray. Insufflation is stopped when the manometer indicates that the pressure has fallen or remains stable for a few seconds, and patency of one tube can be considered present if this pressure level is below 100 mm. Hg. There is little virtue in testing patency at pressures higher than 150 mm. Hg. Rupture of a freshly ligated normal tube has been observed at a pressure of 140 mm. Hg. The use of high pressures to therapeutically "force a block" is more likely to rupture the tube than dilate a stricture.

If patency is not secured, insufflation is repeated at least six times consecutively, allowing several minutes of rest between each trial. In normals, the pressure at which gas enters the peritoneal cavity varies considerably. It has been shown[2] that on repeated insufflation at the same sitting, the gas enters the peritoneal cavity at progressively lower pressure levels. Normal patients may present "closed tubes" at one time, using all criteria including x-ray to be reinsufflated at later dates and demonstrate normal patency. Neurogenic and humoral factors unquestionably play a role.[3] To eliminate "spasm," reassurance is frequently of more value than antispasmodic drugs. To establish the diagnosis of organically closed tubes requires failure to secure patency upon repeated insufflations. For these reasons, caution must be exercised before ascribing therapeutic benefits to either forced insufflation or other moduli of therapy merely because single observations revealed that the tubes were closed prior to treatment to be found open after therapy.

As would be mechanically expected, there would be a small group of cases wherein our manometric criteria would indicate closure, although the patient subsequently suffers "shoulder pain" or has roentgen evidence of subphrenic air. In the absence of defective valves permitting sudden surges of gas flow, these cases must be classified as "patent to some gas" but not patent enough for the passage of a fertilized ovum. This group would automatically disappear if only small quantities of gas are insufflated.

The Kymographic Tracing

Until recently, Rubin used two types of apparatus to record the fluctuations in pressure secured during continuous insufflation. One comprised an ink writer floating upon the column of mercury in the open manometer and the other, the Grafax model, has an ink-writing lever activated by an aneroid manometer. Both machines displayed considerable lag and required large volumes of gas for recording. On test, approximately 68 c.c. of gas were needed to drive the mercury recorder from the base line to a level indicating 200 mm. Hg., while 25 c.c. sufficed for the Grafax model. At a flow rate of 60 c.c./min., machine artifacts become considerable. In 1943, he mentioned but did not describe two modifications.[4] In one, the volumeter was apparently eliminated, while pressure was recorded by the Grafax anaeroid. In the other, recording was secured by

a "photo-electric" system. In 1942, Mayer and associates[5] used an optical drum on the Wiggers principle with excellent sensitivity. The objection to this apparatus is the necessity of working in a darkened room and the difficulty of following pressure variations during the experiment.

To obviate these difficulties, a recording insufflator was constructed on the principle of the "strain gauge." Briefly described, the strain gauge operates on the principle that the resistance of a wire is affected by the mechanical strain induced in it. A suitable gauge was applied to the surface of a tiny copper-beryllium drum which in turn was joined by narrow brass piping to the

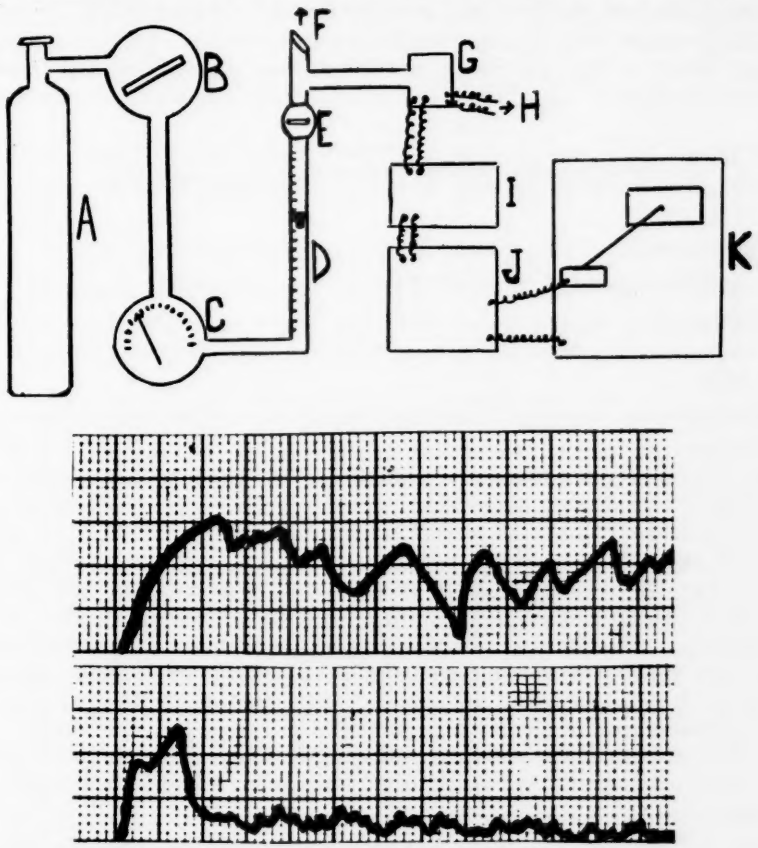

Fig. 1.—Schematic plan of apparatus and two typical tracings secured in normal women. *A.*—tank of gas under 600 pounds' pressure; *B.*—reducing valve; *C.*—gauge indicating pressure of gas delivery; *D.*—rotameter with float; *E.*—valve controlling rate of gas flow; *F.*—tube leading to patient; *G.*—strain gauge; *H.*—bridge voltage, 5 volts, 60 cycle A.C.; *I.*—carrier amplifier; *J.*—rectifier and filter; *K.*—direct writing oscillograph.

Rotameter. Changes in pressure within the system deformed the drum and induced strain in the gauge. With suitable rectification and amplification, a record of change in resistance and therefore of pressure was obtained by a direct writing oscillograph (Fig. 1). Under test rates of flow of 10 c.c. of gas per minute, thirty full swings of the recorder, registering a span of 200 mm. Hg., could be obtained, whereas barely two are obtainable under similar conditions with the Grafax model.

The tracings secured by all types of apparatus during insufflation of humans or animals present several features in common:

1. A primary rapid rise in pressure followed by an abrupt fall which is called the primary pressure peak.

2. A plateau of sustained pressure about which fluctuate major and minor waves of pressure. The major and minor waves differ in character as well as amplitude. The rate of climb of both types of waves and of the primary pressure peak parallels each other but is slower than that secured on simple mechanical obturation of gas escape from the apparatus. The rates of fall in pressure of the minor waves tends to be rapid and abrupt, and almost equals the rate of fall observed when the escape of gas is suddenly released from the system. The rate of fall of the major waves is distinctly slower.

A comparison of the tracings secured by the Grafax model, mercury float, and the strain gauge reveal surprisingly few differences. The strain gauge which is the most sensitive displayed no greater frequency of waves, but the amplitude of all waves tended to be much greater with falls almost or to the base line.

Four possibilities are present to explain the origin of these rhythmic waves of pressure. The fluctuations may be due to resistances produced by:

1. Contractions of the uterus with the tubes acting as passive agents.

2. Contractions of the tubes with the uterus completely quiescent.

3. Contractions of the tubes with the wave of contraction originating in the tube but sweeping over the uterus which contracts synchronously or shortly after the tube.

4. Independent, unrelated contractions of both tubes and uterus.

Categorically, the waves of pressure recorded by the mercury float or Grafax apparatus cannot be produced by uterine contractions with the tubes acting as passive, hoselike channels. Pressure changes recorded by these machines require such a large volume of gas that approximately 0.35 c.c. of gas must be displaced to register a wave of pressure of 1 mm. Hg. A cannula was introduced into the uterus of a rabbit so close to its uterotubal junction that the uterine cavity volume was reduced to a volume of less than 0.2 c.c. With a Grafax model, usual type of tracing was still obtained with waves of pressure of ten or more millimeters being recorded. The strain gauge will record pressure variations of 1 mm. with but 0.01 c.c. of gas displacement, but the frequency of waves obtained on experimental insufflation does not increase. Additional evidence was obtained[5] by driving radiopaque fluid through the human uterus and tube and in these experiments, tubal contractions were always detected when the tracing exhibited a rise in pressure.

As to the second possibility, experiment indicates that the uterus is not completely quiescent during insufflation. On ligating the isthmic portion of the tube of a rabbit and distending the uterus with gas, pure uterine contractions can be elicited with the strain gauge at all levels of insufflating pressure, i.e., to 200 mm. Hg. In one of the illustrations in his recent article,[4] Rubin demonstrated uterine contractions at levels of pressure similar to that of the plateau level observed during insufflation.

Reynolds[6] has presented an admirable summary of the work of Westman and others upon direct observations of tubal and uterine contractions in several species, including the rabbit. To quote him, ". . . the motility of the uterus in oestrus is normally governed by the arrival of excitatory waves from the tubes . . . at times other than oestrus, the uterine threshold to excitation of neighboring areas of myometrium by contraction in either the tubes or in various

places of the uterus, is high, although the property of automatism persists and shows itself by weak activity in every part of the organ. . . .'' An experiment was performed to confirm this third possibility, i.e., some of the waves of pressure observed on insufflation originate in contractions of the tube but that the contraction waves sweeps over the uterus as well. Bozler has described the uterine muscle of the rabbit as a syncytium.[7] Under local anesthesia, a rabbit was insufflated according to the technique of Feresten and Wimpheimer[8] with a Grafax recorder. The uterus and tube was drawn out of the abdomen to separate them from contact with adjacent viscera. A pair of electrodes were placed 3 mm. apart upon the midportion of the uterus, and another pair on the isthmic portion of the homologous tube. The electrodes were connected to a two-channel pen writing oscillograph adjusted to record 20 microvolts. The following observations were made:

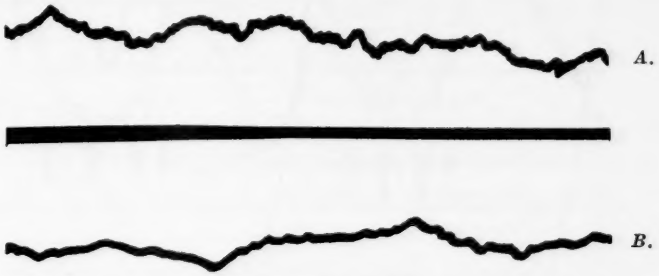

Fig. 2.—Electromyographic tracings of nondistended tube (*A*) and uterus (*B*).

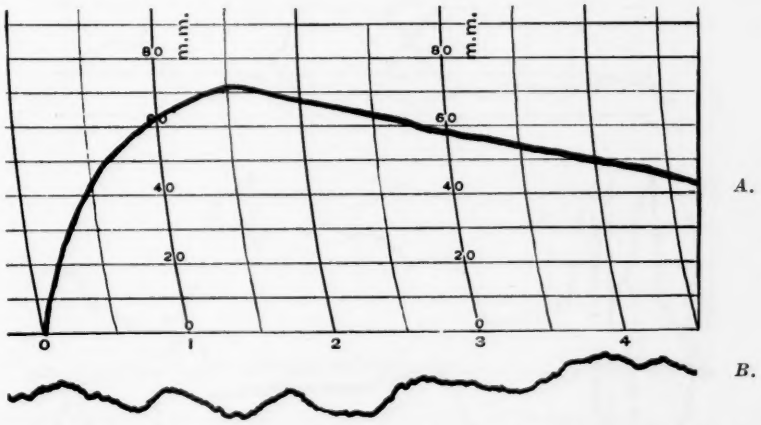

Fig. 3.—Insufflation tracing depicting normal primary peak and plateau with total absence of waves of pressure (*A*) and electromyographic tracing of tube (*B*).

1. Mild evidence of electrical activity was observed in the contracting nondistended uterus and tube (Fig. 2).

2. At the onset of insufflation, a primary pressure peak and plateau were obtained but the plateau, as is frequently seen, was flat without either major or minor pressure waves. The electromyogram during this period revealed little change from that in the nondistended uterus (Fig. 3).

3. After five minutes of continuous insufflation, both major and minor waves of pressure were recordable. Preceding each of the minor waves, tremendous electrical activity in the form of bursts were recorded, whereas the major waves were unaccompanied by any such changes. The type of electrical discharge sug-

1. A primary rapid rise in pressure followed by an abrupt fall which is called the primary pressure peak.

2. A plateau of sustained pressure about which fluctuate major and minor waves of pressure. The major and minor waves differ in character as well as amplitude. The rate of climb of both types of waves and of the primary pressure peak parallels each other but is slower than that secured on simple mechanical obturation of gas escape from the apparatus. The rates of fall in pressure of the minor waves tends to be rapid and abrupt, and almost equals the rate of fall observed when the escape of gas is suddenly released from the system. The rate of fall of the major waves is distinctly slower.

A comparison of the tracings secured by the Grafax model, mercury float, and the strain gauge reveal surprisingly few differences. The strain gauge which is the most sensitive displayed no greater frequency of waves, but the amplitude of all waves tended to be much greater with falls almost or to the base line.

Four possibilities are present to explain the origin of these rhythmic waves of pressure. The fluctuations may be due to resistances produced by:

1. Contractions of the uterus with the tubes acting as passive agents.

2. Contractions of the tubes with the uterus completely quiescent.

3. Contractions of the tubes with the wave of contraction originating in the tube but sweeping over the uterus which contracts synchronously or shortly after the tube.

4. Independent, unrelated contractions of both tubes and uterus.

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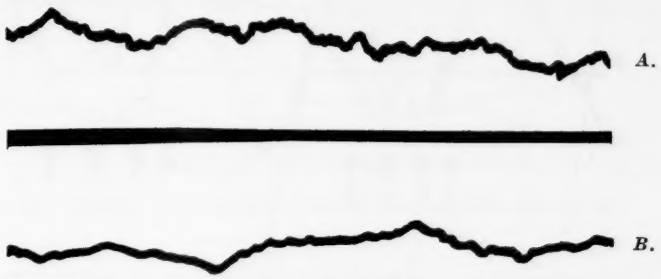

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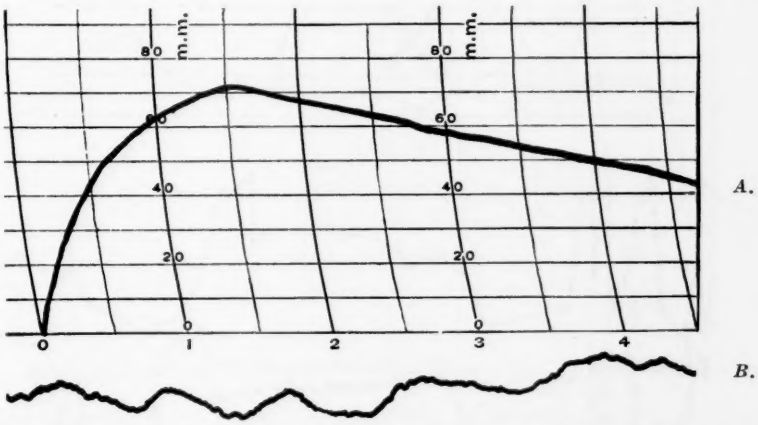

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gested that seen in nerve activity rather than the variety induced by smooth muscle automatism. These bursts were always recorded over both the uterus and the tube (Fig. 4).

4. The animal was killed by the intravenous injection of 50 c.c. of air and reinsufflated. Only major types of pressure waves were observed without any of the minor waves. None of these waves were preceded by the bursts of electrical activity recorded above, and the tracing of the electromyogram resembled that of the nondistended uterus (Fig. 5).

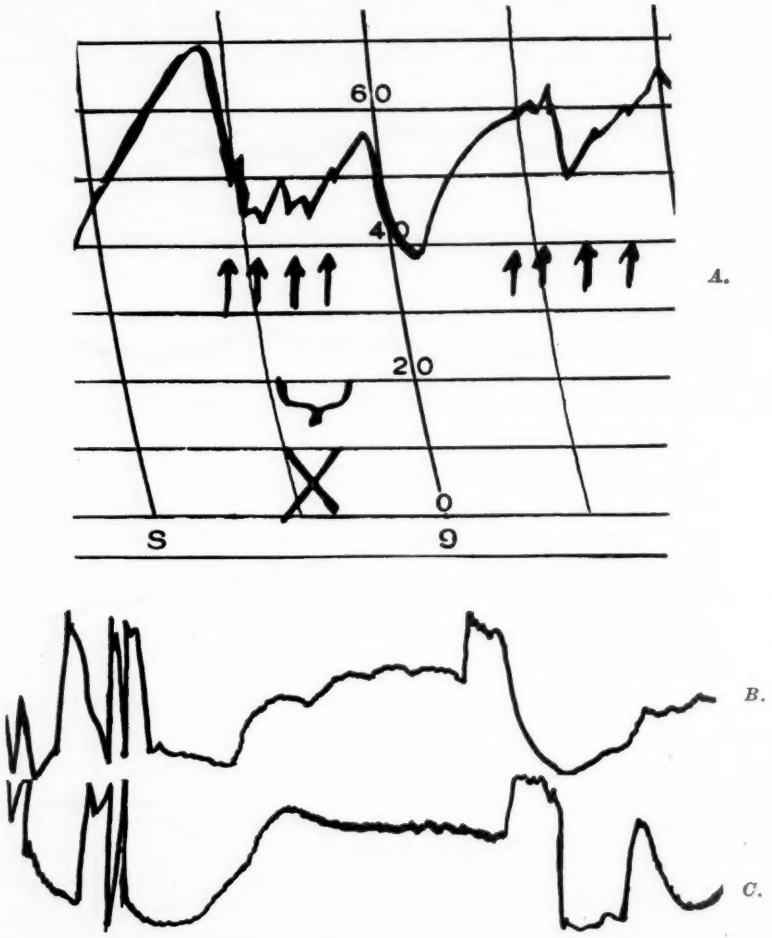

Fig. 4.—Insufflation tracing of same animal employed in Fig. 3, after eight minutes of insufflation with appearance of major and minor waves of pressure (*A*) and electromyographic tracing of tube (*B*) and uterus (*C*) during the period embraced by the bracket.

It is doubtful that the waves of pressure observed on insufflation are produced by unrelated independent contractions of the tube and uterus. In the intact animal, I have been unable to secure electromyographic evidence of uterine contractions sufficient to produce a wave of pressure to insufflation without similar electrical activity in the tube. Numerous observers have commented upon the higher frequency of automaticity of the tube compared to the uterus. Insufficient numbers of animals have been tested during pregnancy and in estrus

and anestrus states, but it is doubtful that the uterus ever acts as the pacemaker for the tube. Certainly with the Grafax or mercury manometer types of recorders, all waves of pressure must be construed as purely tubal in origin. Further electromyographic study would be of interest in an analysis of the neurogenic factors involved.

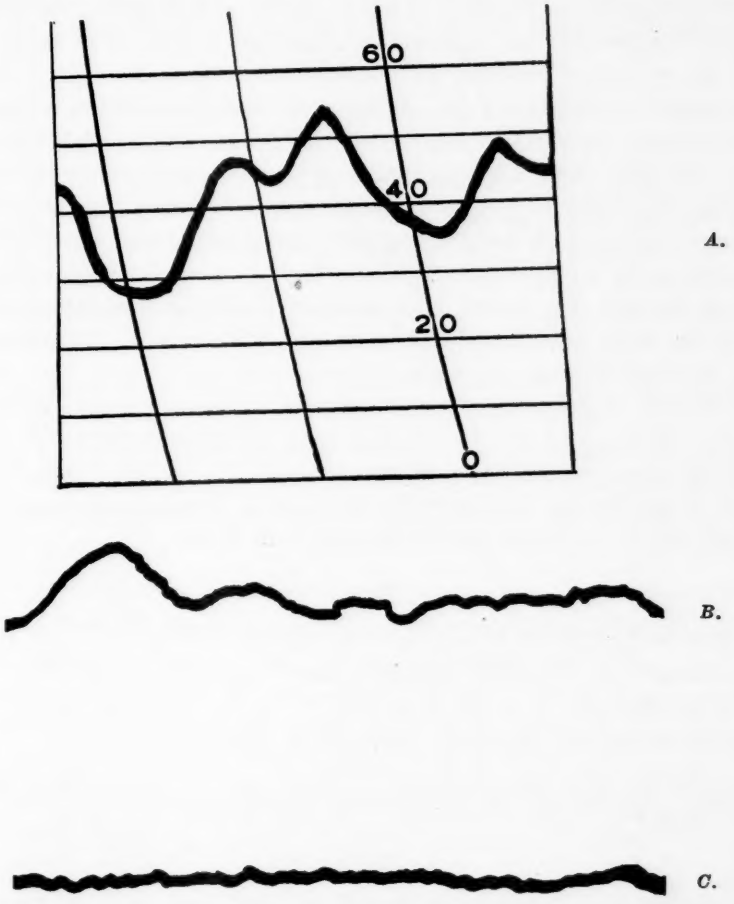

Fig. 5.—Insufflation of dead animal with tracing indicating only major waves of pressure (*A*) and electromyographic tracing of tube (*B*) and uterus (*C*) during this period of insufflation.

I share Rubin's contention that a study of the insufflation tracing may furnish evidence of a strictured tube. Mechanical considerations demand strict criteria for establishing the diagnosis of stricture of the tube. The primary pressure peak and plateau levels must persistently remain above the 100 or 150 mm. Hg level used as an index of patency; the same level or higher must be reduplicable upon repeat insufflation; the insufflation must be conducted long enough to rule out sustained partial "functional closure" or spasm. As a secondary phenomenon, the major and minor waves of pressure might be shallow or absent, for the amplitude of these waves is to some extent inversely proportionate to the plateau level.[2] I have never encountered a clinical case that satisfied these criteria.

I cannot confirm Rubin's claim that adhesions about the tube would produce disappearance of the waves of pressure.[4] It is difficult to reconcile his claim that pins inserted into the seromuscular edge of an extirpated tube cause the rhythmic contractions to disappear with the work of Feresten and co-workers[8] that all of the tube except for minute portions of the isthmus may be removed with little change in the tracing. I have confirmed Feresten's work on numerous occasions. Frequently, one secures an otherwise normal tracing except for absence of the waves of pressure in normal, fertile women or in animals, and if the insufflation is continued for as long as twenty minutes, normal types of waves reappear. Experience in uterine manometrics has shown that as much as fifteen minutes of continuous distention of the uterus may be necessary before uterine contractions become demonstrable. I have never clinically observed a wave-free otherwise normal tracing when insufflation was continued for twenty minutes except in menopausal, normal women. Even in these cases, prolonged insufflation beyond this period and possibly at higher pressures may elicit contractions, for even an atrophied uterus and tube retains some degree of automaticity inherent in smooth muscle.

Insufficient studies have been made to evaluate humoral effects upon the insufflation tracing. Hormonic studies with insufflation possesses no advantage over similar experimentation with the intrauterine balloon, but does retain the potential disadvantage that insufflation in the postovulatory period may hydraulically drive the ovum out of the uterus or tubes.

Summary

1. The technique and criteria for patency determined by uterotubal insufflation have been described, using an improved form of insufflation apparatus.

2. Kymography, of large academic interest, has furnished no additional information as to the pathologic state of the tubes.

The technical advice of Dr. Harold Lamport, Yale University School of Medicine, and Mr. Paul Traugott, Director of the Electro-Physical Laboratory, is gratefully acknowledged.

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ABORTIONS: A STUDY WITH EMPHASIS ON TREATMENT*†

CAPTAIN PAUL PETERSON, B.Sc., M.D., F.A.C.S., MEDICAL CORPS,
U. S. NAVY, BETHESDA, MD.

IT IS impossible at present to evaluate results on known viable fetuses at the time of beginning treatment. However, in these studies, an approach to this has been attained by employment of an Aschheim-Zondek or Friedman test on all threatened abortions. The urine was always collected before active treatment was begun. As will be noted from the results, a very high percentage of admissions were negative, denoting that the fetus had ceased to be viable some ten days to two weeks before abortion threatened. For purposes of drawing more accurate conclusions as to the effects of medication, all cases, including the pregnancy test negative cases, were treated the same way for each group, and no abortion was completed until passage of tissue had occurred.

For purposes of this study, abortion refers to the expulsion of the fertilized ovum any time before a good state of viability is attained, or around the thirtieth week. This is an attempt to remedy those cases which abort, and no obvious cause is detected at the time.

In general, opinions seem to fall into three divisions: (1) abnormalities of the ovum, (2) abnormalities in the maternal developmental environment, and (3) paternal abnormalities.

Having seen only one fetal abnormality in those cases later carried to fetal viability who did threaten to abort under care, leads this author to agree with Mall and Corner that such abnormalities are on an environmental basis.

Malpas concluded that after two successive abortions 62 per cent would have a normal pregnancy; after three, 27 per cent; while after four only 6 per cent, without any specific treatment.

Author's Series

This study has been carried out over a ten-year period, from June 30, 1936, to July 1, 1946, during which time there were 6,105 viable babies and 937 spontaneous abortions under the writer's observation on various Naval Maternity Services to which he was assigned. Approximately 5 per cent of the births were repeats in the same patients. The 937 tabulated abortions represent different persons. This group comprised 235, or 25 per cent of the total, who had aborted three or more times and were classed as "habitual aborters." The others were largely primi-aborters which accounted for 665 or 71.1 per cent of the total, while the second aborters accounted for only 37, or 3.9 per cent of the total. The incidence of abortion in the total 7,042 pregnancies

*Data from the Obstetrical and Gynecological Departments of various U. S. Naval Hospitals. The author is now Head of the Department of Obstetrics and Gynecology, and Officer in Charge of Dependents' Service, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

†The opinions and/or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

was, therefore, 15.35 per cent. It was interesting to note that there was not a single infection to cause concern in this group. Also, there was only one case which hemorrhaged sufficiently to require emergency transfusion. So striking were these two features that the author has come to feel that any severe hemorrhage or severe infection in an abortion should be treated as an induced abortion.

Of the 937 who aborted, 356 were lost before studies were completed. A thorough preconceptional study was carried out on each of the remaining 581. This study and the management of the cases have improved in the light of newer knowledge and the discovery of newer medicine and biologicals. Out of this completed group, 520 or 89.5 per cent were carried through a successful pregnancy after the study. In the completed group there were 153 habitual aborters, which was 27.3 per cent of the group. Of these habitual aborters, 64.1 per cent were carried through to a period of viability, though many not to full term. This 64.1 per cent success, though far from the desired results, is certainly encouraging in the face of an outlook of about 27 per cent if not treated.

Among the 581 cases which were completed, there were 292, or 50.3 per cent, pregnancy test negative on admission. Most of those with positive tests were later found to have retrodisplaced uteri, infantile uteri, low prothrombin levels, and some low estrogen levels. This percentage of positive tests is quite low as compared with what might be expected if all cases were included who did not actually abort as these patients did. Practically all those with low pituitary function, low progesterone, or low estrogen-progesterone levels, and some low estrogen level cases were negative on admission. Undoubtedly, many women who have nidatory bleeding will go ahead and carry through without treatment.

TABLE I. INCIDENCE

CONDITIONS	NO. CASES	PER CENT	REABORTERS	PER CENT
Infantile uterus	77	13.2	4	5.2
Retrodisplaced uterus	158	27.2	2	1.2
Low prothrombin level	19	3.2	0	---
Low estrogen effect	168	28.9	0	---
Habitual aborters				
Low pituitary effect	37	6.3	2	5.4
Low progesterone effect	54	9.3	26	48.1
Low estrogen-progesterone	68	11.7	27	39.4

Table I lists the conditions which existed and were thought to have been responsible for the abortion in the completed group. The table also shows those who aborted again under preconceptional and continued treatment.

Thus, it can be seen that 442, or 72.7 per cent, were not habitual aborters. In this group all were carried through the next pregnancy with the exception of six cases for a 98.6 per cent success. The degree of success here seems quite high, but it must be remembered that this group is one in which a high percentage would carry through anyway, and the treatment is merely an aid. However, in the habitual abortion group it is felt that treatment has accomplished something worth while. It may be noted that the low pituitary group who are still able to become pregnant offer a very good prognosis under therapy, but usually a very poor one without it. The low progesterone group seems to offer the least hope.

Causative Factors

In the series here presented there were no abnormalities attributable to tumors, infections, or lacerations of the cervix. Neither did thyroid dysfunction alone seem to play a part, although the general well-being of the patient was improved if given when indicated. There were no abortions which could be directly traceable to alcohol, lead, diabetes, or incompatibility of the Rh factor.

No patient bleeding during the first five months was found to have anti-Rh antibodies, but tests were run only during the last few years of the study. The paternal influence could not be evaluated in this series, but it would seem that only in the very unusual case would it play a part, and, therefore, may be considered negligible. This study has led the author to feel that the causes may be listed as: (1) maternal or environmental, and, (2) ova with defective germ plasm. The latter cannot be disproved from this study, but the indications are that it plays no part except perhaps in the very rare case.

Vitamin Effect.—Moore and co-workers, by feeding a diet deficient in vitamin K, observed abortion in all animals.

Javert and Stander found deficiency in vitamin C in 69 per cent and deficiency in vitamin K in 72 per cent of pregnancies studied. Both were low in 61 per cent.

In the writer's experience, abortion will occur with prothrombin levels of 50 to 60 per cent of normal, and bleeding frequently occurs with levels as high as 85 per cent of normal. In his experience vitamin E has been of no demonstrable value at all. No cases with low vitamin C alone aborted in this group which were studied for vitamin C levels.

Progesterone Effect.—Progesterone, in the author's experience, has not relieved cramps in women threatening to abort; in fact, many were made worse. It was felt that injecting progesterone would depress the luteinizing hormone from the pituitary and could actually do harm in the long run. Results have been much improved since omitting progesterone, except where definitely indicated by preconceptional study.

Estrogen Effect.—Interdecidual bleeding during the first six weeks, and perhaps later, is many times due to spasm of the spiral arterioles and subsequent relaxation. From the action of estrogen on the vessels it is obvious that it would be more efficacious. These cases will probably stop bleeding anyway.

From endometrial studies following estrogen therapy in nonpregnant women, this author feels that estrogen depresses FSH while at the same time stimulating production of LH. If this is true, the estrogen therapy seems more rational, especially if any treatment is to be used empirically.

Gonadotrophic Hormone Effect.—There is evidence to show that there is an increased concentration of pituitary gonadotrophic hormone in the urine of pregnant patients from the sixth to the twelfth or thirteenth weeks of pregnancy.

I found a direct relationship between the low glycogen content of endometrium and vaginal mucosa and low gonadotrophic hormone secretions. Many of these cases who did not abort under observation had negative pregnancy tests until as late as three months of gestation. The gonadotrophic hormone is found to be highest during the vomiting stage. In those patients who do not vomit, there is a mild to a marked reduction in the serum gonadotrophic hormone.

Deficiency of chorionic gonadotropin is not a frequent cause of corpus luteum failure, since it was below the normal range in only one of 19 cases tested by Vaux and Rakoff in their series. This is an incidence of 5.25 per cent as compared with an incidence of 6.3 per cent in the author's series (see Table I, "Low pituitary function").

Estrogen-Progesterone Effect.—Vaux and Rakoff found a high percentage of habitual aborters who exhibited low pregnandiol titers, and diminished blood and urine estrogen levels occurring any time during pregnancy.

Diagnosis

Usually the physician is handicapped severely when a patient is seen for the first time during a threatened abortion. With absolute rest and quiet a prime indication, he is extremely limited in his examinations, and usually treats empirically without due regard for the cause of the abortion. Therefore,

if one is to obtain best results, the patient must be thoroughly studied when she is not pregnant, and then be advised to become pregnant at the optimum time.

It has been the author's practice to give each patient who has previously aborted a thorough study, including a good history, basal metabolic rates, glucose tolerance studies, Rh factor studies, etc. The physical examination alone will reveal such defects as infantile uterus, or retrodisplacements of the uterus. A prothrombin level is taken on all patients, preferably during a menstrual period. Also, any pregnant woman who bleeds has a prothrombin level estimation made. Since earlier studies the author has ceased to make checks on the vitamin C levels. The low prothrombin level patients complain of general sluggishness and weakness. This same feeling of poor well-being is found in low pituitary function cases, but is readily relieved by a 20 per cent protein diet, whereas the low prothrombin level patients are not.

A history of frontal headaches which are noted usually upon arising and wearing away with the day, and edema before menses or in the previous pregnancy are indicative of low estrogen level. A history of failure to be nauseated is indicative of less than average gonadotrophic factor.

Endometrial biopsies are taken for study of the endometrium along with vaginal smears. These can be checked with estrogen and pregnandiol determinations on the urine also, but is not practical as yet, and was used in very few cases in this study.

These studies have shown that from biopsies and vaginal smears one may determine estrogen and progesterone effect with a fair degree of accuracy; sufficiently so for practical purposes. This, however, is not the whole story, since the cause in each case may be different. Glucose tolerance and glucose-adrenal tolerance curves will aid in determining if the pituitary function is low. There is also the feeling of generalized weakness and lassitude. There is an increasingly low basal metabolic rate. These findings along with biopsies and vaginal smears indicating low estrogen-progesterone effect will give a diagnosis of low pituitary function as the primary factor. Also, in early pregnancy these cases show low serum gonadotrophic titers, if one can run them. On the other hand, a low estrogen-progesterone effect without the evidence of pituitary disturbance will indicate either refractory ovaries or refractory endometrium. Here the differentiation can be made accurately by estrogen and pregnandiol studies, theoretically.

In those few cases with physical abnormalities and endocrine abnormalities, both conditions were corrected, but the case was listed under the endocrine condition as it was thought to be the more serious of the two conditions.

Treatment

Treatment resolves itself into three periods: (1) preconceptional, (2) postconceptional, and (3) period of threatened abortion.

The treatment in this series was directed primarily at the factor to which the previous abortion was attributed. They were all given the usual general instructions. Since observation with their previous abortion had indicated that transportation to the hospital aggravated the condition, all were instructed to go to bed immediately should they develop the least vaginal bleeding or uterine cramps. The attending physician was to be notified at once. The patients were not removed to the hospital until (or unless) they passed tissue which was shown to the physician. No complications arose to cause regret of this procedure, as only one hemorrhaged sufficiently for alarm, and none became infected.

The preconceptional and postconceptional treatments for the responsible factors were as follows:

Infantile Uterus.—These patients were given 0.5 mg. of diethylstilbestrol in the first half of the cycle, followed by 10 mg. of progesterone daily (orally) and

1 mg. of diethylstilbestrol following estimated ovulation to within three and five days, respectively, of the expected menses. This was given for three consecutive months, then omitted for three months. At the end of the first three months' period a dilatation and curettement was done for endometrial studies, and to further stimulate the uterus. Another curettement was done at the end of the second three months when medication was again begun and the patient allowed to become pregnant. When the first period was missed, the hormones were discontinued so as not to interfere with the normal gonadotrophic secretions of the pituitary.

Postconceptional and threatened abortion period treatment, other than general precautions, is felt to be useless. Many of these patients spotted slightly for short periods.

Retrodisplacement of the Uterus.—These patients were advised to wait for three months. At the end of this period the uterus was replaced and a pessary inserted if the uterus were movable. If it were immovable, it was replaced surgically under anesthesia, all adhesions severed, and the pelvis well peritonealized. The pessary was left in place for the first three months of pregnancy. It was felt that the Findley type pessary was superior to others, as it caused less manipulation and trauma to the patient when removed for cleaning. Putting in a pessary and replacing a uterus once the patient is pregnant as well as the knee-chest position and "monkey walk" have all proved hazardous procedures in the author's hands.

Treatment during the threatened abortion period consisted of general measures plus having the patient remain on the abdomen in bed, or, where possible, slowly filling a mercury bag in the vagina. Usually it was found that the pessary had failed to hold the uterus in complete reposition after the weight of the pregnancy was added.

Low Prothrombin Level.—These patients were advised to wait three months. During the week preceding each menses they were treated. In the early cases, before synthetic preparations were available, cabbage juice was given in large amounts. Later, 2 mg. of a good synthetic vitamin K preparation were given intravenously daily for six days. This was continued at monthly intervals after conception so as to precede the menstrual time. If spotting occurred, the medication was immediately begun in 4 mg. doses daily, intravenously, until the prothrombin level was maintained at 100 to 110 per cent of normal. The bleeding was slow to stop once begun, but these patients were found not to abort readily in spite of the bleeding, if the prothrombin levels were kept up. In this group a great deal can be done during the threatened abortion period if the true condition is recognized.

Low Estrogen Effect.—These were advised to wait three months. During this period they were given 0.5 mg. of diethylstilbestrol during the proliferative phase, and 1 mg. during the secretory phase up to five days of the expected menses. When they began trying to become pregnant the drug was continued in 1 mg. doses without interruption. If pregnancy did not occur the menses usually came on time. If the menstrual period were a week late, the medication was increased to 5 mg. daily and increased by 5 mg. every two weeks until about the beginning of the seventh month, and then reduced by 5 mg. every ten days until completely withdrawn or delivery occurred. If not withdrawn by three weeks before the expected date of confinement, these patients usually went past term. If any symptoms of low estrogen or bleeding occurred, the dose was increased by 5 mg. daily until symptoms were relieved. These cases appear to be relatively easily controlled, and only a low per cent even spotted. It is felt that large doses of estrogen given immediately bleeding occurs may be beneficial in the period when abortion is threatening in cases of this type who have not been treated previously.

Low Gonadotrophic (Pituitary) Effect.—This group comprises the most amenable group of habitual aborters. They were treated for a period of three months preconceptionally. In this period, treatment consisted of giving 300 units of chorionic gonadotrophic hormone twice weekly during the secretory phase of the cycle as well as 0.5 mg. of diethylstilbestrol daily during the proliferative phase, increased to 1 mg. plus 10 mg. of progesterone daily during the secretory phase up to within five days and three days, respectively, of the expected menses. When pregnancy occurred the diethylstilbestrol was increased to 5 mg. twice daily and progesterone to 10 mg. three times daily with parenteral injections of each in case of spotting. The chorionic gonadotrophic hormone was increased to 500 units twice weekly. This was in an effort to stimulate better luteinization of the corpus luteum, plus plain substitutional therapy. The substitution part of this routine undoubtedly depresses the remaining pituitary function somewhat, but the gonadotrophic factor seems to compensate for the depression since the results are quite encouraging. This treatment should be kept up until approximately five months of gestation, when it is felt that the placenta will carry the load until about seven months when the treatment should be started again and continued for six weeks or until labor intervenes. A large number of these cases have premature labors, but if treatment is started again at seven months usually they are carried to good viability. Throughout the preconceptional period and during the pregnancy these patients are kept on a 20 per cent protein diet, with special emphasis on a protein meal just before retiring at night. The diet is thought to be most important. One has to be a bit more liberal with the weight gain in these patients as a rule, but toxemia has not been seen to occur in any of them, and fluid balance usually is maintained easily with the diet.

For some reason, perhaps due to pituitary enlargement during pregnancy, subsequent pregnancies in these patients seem easier, usually each one going a little nearer to term. It is not felt that treatment begun in the threatened abortion period will be of much value. If antibodies were formed to the gonadotrophic hormone it was not evidenced clinically, but tests for them were not carried out.

Low Progesterone Effect.—The results in this group have left much to be desired, and it is felt that further studies may lead to better results. In the preconceptional period of three months the patients were given 300 units of chorionic gonadotrophic hormone twice weekly with 10 mg. of progesterone daily during the secretory phase of the cycle. Ephynal acetate (formerly wheat germ oil was used) was given daily in 25 mg. doses to gain whatever effect its similarity of action to progesterone might offer. These patients do not seem to conceive quite as readily as those in the previous group. After conception, the chorionic gonadotrophic hormone was increased to 500 units twice weekly, and the progesterone to 10 mg. three times a day orally. The ephynal acetate was increased to 50 mg. daily. This was continued without interruption up to the period of viability and then stopped. These patients seem to abort at any time during the pregnancy in spite of the placental effect. It is felt that perhaps diethylstilbestrol might have helped in these cases, for its tendency to stimulate the LH factor of the pituitary, and might counterbalance the depressing effect which the progesterone must have on this factor. The treatment during the threatened abortion stage will not be of value if previous treatment has not been given, as most all of these showed negative pregnancy tests on admission to the hospital. Also, missed abortion seems more common in this group.

Low Estrogen-Progesterone Effect.—This group proved to be but slightly more amenable to treatment than the preceding one. These patients were treated from three to six months preconceptionally, and until there was some response

to treatment as shown by vaginal smears and endometrial biopsies taken during both proliferative and secretory phases. They were given 5 mg. of diethylstilbestrol three times a day and 10 mg. of progesterone three times a day on the twenty-first, twenty-second, and twenty-third days of the cycle for at least three months consecutively. When the patient was advised to become pregnant the medication was changed to diethylstilbestrol 0.5 mg. daily during the proliferative phase, increased to 1 mg. during the secretory phase plus 10 mg. of progesterone daily. Urines were collected at five-day intervals for pregnancy tests. As soon as a positive test was obtained the diethylstilbestrol was increased to 10 mg. daily and progesterone to 10 mg. three times a day. The treatment was continued three to four months as it did not seem necessary to continue longer. A few of these patients had premature deliveries but usually at a viable age for the fetus. It is felt that without preconceptional therapy, treatment during the threatened abortion period would avail little even though many of these were still pregnancy test positive on admission. The treatment would hardly improve the decidual state in time to hold the pregnancy except in very rare instances, perhaps, and then environmental effect on the ovum might cause abnormalities of the fetus.

At first it was rather surprising that the results in this group were somewhat better than in the preceding which was principally a low progesterone effect. However, actually, the level is not always low in this group, but in many the uterus required a higher than average level before it would respond, while in others the ovaries failed to respond properly to the gonadotrophic hormone. The results in this latter subgroup parallel very closely those of the low progesterone effect group, while the results in the former subgroup respond quite well to treatment, and are responsible for the increased results in this group as a whole. Unfortunately, the exact results cannot be expressed in percentages since this group was not broken down into subgroups until a considerable time after the studies were begun.

Summary

This communication is a study of abortions over a ten-year period from June 30, 1936, through June 30, 1946, covering some 7,042 pregnancies with 937 spontaneous abortions for an incidence of 15.35 per cent. Of these cases, 356 were lost before the studies were completed. Twenty-seven per cent of the completed group were "habitual aborters" by accepted standards.

The abortions were grouped as in Table I.

Among the group completely studied, there were only 49.7 per cent pregnancy test positive, but this group included only those who actually aborted.

The success with the habitual aborters was 64.1 per cent as against an untreated expectancy of some 27 per cent. The success with the nonhabitual aborters was 98.6 per cent.

The success and failure by groups have been given in Table I.

Basically, the cause of abortion is, in all probability, environmental, but defective ova cannot be ruled out by this study.

The treatment was divided into: (a) preconceptional, (b) postconceptional, and (c) threatened abortion period, and according to the indications manifested by the cause.

Conclusion

This study has shown that for best results in the treatment of abortion, and especially the habitual aborters, a thorough preconceptional workup is necessary. The habitual aborter is such from the first abortion, depending on the hormone imbalance, and not simply because nothing has been done until she has aborted three or more times. Especial attention should be given to the endocrine balance as well as to physical defects and vitamin deficiencies. For best results, treatment must be begun preconceptionally, and continued post-conceptionally, as well as when abortion threatens.

Further study along these lines should improve the results with those of the low progesterone and low progesterone-estrogen groups especially.

A check on all patients with a recognized pregnancy test showed that without the above studies and treatment not more than approximately 50 per cent of the abortions can be salvaged no matter what is done. This does not include bleeding from nidation and certain cases of spasm of the spiral arterioles which will likely carry through regardless of the treatment, or whether treated at all.

From this study one may conclude that habitual aborters fall into three distinct groups according to endocrine deficiencies.

No one medication or combination of medications will prevent all abortions, and until this is recognized and steps taken to individualize each case best results will not be attained.

It should be remembered that when chorionic gonadtropins are used preconceptionally, the pregnancy test becomes unreliable when pregnancy is suspected.

An interesting observation was the fact that patients treated with diethylstilbestrol for low estrogen effect alone usually went beyond term if the medication were not stopped at least three weeks before the expected date of confinement; and, also, those patients with low progesterone effect alone comprised the group in which missed abortion occurred. This would seem to indicate that the estrogens play the more important part in the onset of labor.

It has been shown also by these studies that diethylstilbestrol has a much stronger and more direct effect than the natural estrogens which were used early in this study.

The author wishes to express sincere appreciation for helpful suggestions for various aspects of this study to the following: Captain J. E. Porter (M.C.), U.S.N., Ret.; Dr. C. L. Buxton and Dr. C. P. O'Connell, former Naval Reserve Medical Officers; and Dr. Theodore Neustaedter of the New York Post-Graduate Hospital.

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PLASMA VITAMIN A LEVELS IN PREGNANCY

Relationship to the Total Plasma Lipids*

DAVID CAYER, M.D., VICTOR CRESCENZO, M.D., AND SOPHIA CODY, M.A.,
WINSTON-SALEM, N. C.

(From the Department of Medicine, Bowman Gray School of Medicine of Wake Forest College)

LABORATORY procedures for the measurement of vitamin levels have been developed in the past few years, and are now fairly well standardized.[1] As a result of studies employing these procedures, nutritional requirements are better understood, and the minimum dietary levels thought to be necessary for good health have gradually been lowered.

It is generally stated that the need for vitamin A is increased during pregnancy, and that few pregnant women receive adequate amounts of this vitamin in their diets.[2] The information which has been compiled to show the inadequacy of such diets, however, compares poorly with the clinical evidence of vitamin A deficiencies. The purpose of the present study was twofold: (1) to evaluate clinically the frequency of vitamin A deficiencies in a group of apparently normal gravid patients receiving no specific diets or vitamin supplements during pregnancy, and (2) to study the relationship of the total blood lipids to the vitamin A levels of the plasma.

Most of the recent studies on the relationship of the blood lipids and the levels of vitamin A in the plasma have been concerned chiefly with the alteration of the blood lipids which occurs when the intake of vitamin A is varied, and with the influence of large test doses of vitamin A on the blood lipids. The results of these studies are controversial. Josephs,[3] using rats, found that the ingestion of large amounts of vitamin A caused little rise in the serum level of vitamin A when the blood lipids were low. Others[4] have reported that hyperlipemia is a frequent, although not a regular, accompaniment of avitaminosis. The drop in the levels of lipids and vitamin A in the plasma during acute infectious diseases has pointed to the apparent relationship of these two substances, and a number of investigators have suggested that the blood lipids might serve as a vehicle for the transportation and storage of this vitamin.[5]

Most instances of hyperlipemia are secondary to abnormal metabolic and physiologic states, such as diabetes, ether, or chloroform narcosis, renal or liver disease, and blood dyscrasias. A study of the relationship of total plasma lipids to vitamin A concentrations in pregnancy provides an opportunity to observe the changes in the level of vitamin A which occur with hyperlipemia developing in otherwise normal individuals under physiologic conditions.

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Material and Method of Study

It was felt that in a study of this nature repeated observations of the same group of subjects would be the procedure of choice in order to minimize the variation known to occur between individuals. This variation is particularly wide in the plasma lipids; a value of half the average may occasionally be found in an otherwise normal individual, and appears to have no significance as regards well-being. It is importnt, therefore, to know how widely the plasma lipids in a single individual vary from time to time. Unless this factor is known, no values found can be considered abnormal unless they are outside the normal limits for a given species.

The subjects of this study were unselected and were taken at random from a group of patients in the middle and upper economic brackets.* No evidence of any chronic, debilitating, or organic disease was present in any of the group studied, and no complications of pregnancy were observed. All patients were given routine dietary and prenatal instructions, but no further attempt was made to evaluate each patient's diet. No patient who received any vitamin supplement was included in the study.

The obvious difficulty of registering women early in pregnancy made the number of cases studied during the first trimester smaller than the others. Of the total group of 26 patients, only 16 were observed during all three trimesters; three more were added during the second trimester, and seven during the third. Sixteen of the group were studied during the puerperium. The determinations of the lipid and vitamin A content of the blood were made once during each trimester, and the postpartum period on blood specimens drawn one to two hours after breakfast. It has been shown that ordinary meals cause no measurable increase in the concentration of vitamin A in the plasma for two to six hours. Boyd took samples of blood three to four hours apart during a twenty-four-hour period, and found that the concentration of plasma lipids is not markedly affected by the time of day, the ingestion of ordinary meals, or sleep.[6]

The photocolorimetric method of Kimble[7] was used to determine the values for vitamin A and carotene in the blood plasma. The total lipids were extracted from the plasma with alcohol, alcohol-ether, and chloroform, and weighed according to a procedure previously described.[8]

Results

The changes in the plasma levels of lipid and of vitamin A observed during pregnancy and the puerperium are summarized in Table I. During the first trimester of pregnancy the mean plasma vitamin A level for the 16 patients studied was 106 international units. This value approximates the levels previously found and reported in the larger series of normal nonpregnant women.[1] The mean value for total lipid concentrations was 607 mg. per 100 c.c. This compares favorably with the figures reported by Boyd, who found the plasma of normal young females to contain an average of 689 mg. of total lipid per 100 c.c., and by Herrmann and Neumann, who obtained an average value of 590 mg. per 100 c.c. in normal nonpregnant females.[9]

During the second trimester 19 patients were studied. The plasma vitamin A levels ranged from 70 to 178, and the mean had risen to 123 international units. The total lipids ranged from 604 to 988 mg. per 100 c.c., the average being 760.

Twenty-six patients were studied during the third trimester, the majority in the thirty-sixth week. The plasma levels of both vitamin A and total lipids showed a moderate decline, although both still remained well within normal

*The authors wish to acknowledge the cooperation of the Department of Obstetrics in the study of these patients.

limits. The vitamin A values ranged from 72 to 142, with a mean of 102. The lipid determinations showed a marked variation, ranging from 288 to 966. Eighty per cent of the values, however, fell between 600 and 950 mg. per 100 c.c. The mean value of 691 is comparable to that found by Herrmann and Neumann in patients near the end of pregnancy—780 mg. per 100 c.c.

The final values were determined on 16 patients during the puerperium, usually between the tenth day and the sixth week after delivery. The plasma vitamin A and total lipid levels were again rising, the latter reaching a mean of 843 mg., the highest level observed during the period of study. The rise in the plasma lipids between the first and second trimester, and that occurring post partum were statistically significant.* The vitamin A level showed a marked degree of constancy throughout pregnancy, the highest level occurring during the second trimester, followed by a moderate decline during the third and a gradual postpartum rise. Statistically, there was no significant difference between any of the means. A study of Table I shows that the mean lipid de-

TABLE I. PLASMA VITAMIN A AND TOTAL LIPID VALUES

TIME OF STUDY	NUMBER OF PATIENTS	VITAMIN A (I.U.)	PLASMA LIPIDS MG. PER 100 C.C.
1 to 3 months	16	Range 72-180 Mean 106	Range 388-990 Mean 607
4 to 6 months	19	Range 70-178 Mean 123	Range 604-988 Mean 760
7 to 9 months	26	Range 72-142 Mean 102	Range 288-966 Mean 691
Post partum 10 days to 6 weeks	16	Range 66-164 Mean 110	Range 560-1084 Mean 843

terminations parallel those for vitamin A, although the highest values for lipids were found during the puerperium.† In the group studied. no single patient at any time was found to have an unusually low plasma value for vitamin A.

The amount of carotene in the plasma was determined along with the level of vitamin A, and was found to range from normal to high. It apparently bore no relation to the plasma levels of vitamin A or of lipid.

Discussion

Plasma Vitamin A Levels.—It is generally agreed that a high blood level of vitamin A indicates an adequate dietary intake and, as a rule, adequate storage; and that a low level in the plasma is an index of a vitamin A depletion. In persons on their usual diets there is little diurnal variation in the plasma levels of vitamin A, and in normal adults months are required to decrease the level of vitamin A in the plasma by withdrawing it from the food. The level of A in the plasma will be reduced by decreased intake, interference with absorption, or increased metabolism, and occasionally by abnormal excretion or mobilization. The decrease in the plasma level of the vitamin precedes clinical evidence of a deficiency.

It has been accepted that pregnancy increases the need for vitamin A, and that the amount of vitamin A required by the body is higher during the post-

*The authors are indebted to Dr. C. N. Herndon for statistical criticism of the results. The "T" test was used for judging the significance of difference between means.

†The relationship of the values is shown in the scatter graph (Chart 1) where a significant correlation between the vitamin A and total lipid values was found (Correlation coefficient = 0.522 ± 0.129).

partum period and lactation than at any other time. The Food and Nutrition Council advises an intake of 6,000 international units daily during the last half of pregnancy, and 8,000 international units daily during lactation. It has been said that few women receive adequate amounts of vitamin A during pregnancy, and Williams and Fralin report that 96.5 per cent of a *selected* group of pregnant clinic patients failed to obtain 6,000 international units of vitamin A daily.[2] Other writers have suggested that the low plasma levels of vitamin A found in pregnant women justify the administration of this vitamin during the latter part of pregnancy. The incidence of vitamin A deficiency in pregnancy is not known. Clinical manifestations of this deficiency, however, are uncommon.

In human beings, low plasma levels of vitamin A can and do exist without recognizable evidence of a deficiency. Therefore a low level of vitamin A in the plasma is not diagnostic as an *absolute* deficiency. In a previous study of 25 patients taking an inadequate diet, blood plasma levels of vitamin A as low as 50 international units per 100 c.c. were found. Although these patients presented clinical evidence of a B complex deficiency, as manifested by oral and lingual changes and peripheral neuritis, none were found to have any clinical evidence of a vitamin A deficiency—that is, no eye changes, night blindness, or follicular keratitis.[1]

In 12 patients with sprue, who lost large amounts of fat-soluble substances in the stool as a result of steatorrhea, plasma vitamin A levels as low as 12 international units were found, and the mean for the group was 48.[10] Nothing to suggest a vitamin A deficiency was observed clinically in any of these patients.

Milam and Anderson, in a nutrition survey of an entire North Carolina rural county, found that only 40 per cent of the persons studied ingested the recommended amount of 5,000 international units of vitamin A daily.[11] In this entire survey, however, less than 1 per cent of the persons had plasma levels lower than 50 international units per 100 c.c.

The mean values of plasma vitamin A for the patients in this study were well within the generally accepted normal range throughout pregnancy. Some of the plasma levels, however, were as low as 70 international units. There was nothing to suggest clinically that the nutritional state of these persons was any less satisfactory than that of those having higher levels, or that the lower value had any influence on pregnancy, delivery, the development of complications, or the postpartum course. Little difference was noted in the vitamin A level between the mothers who were nursing infants and those who were not.

These findings and the postpartum rise in the plasma vitamin A without dietary additions or vitamin supplements suggest that the figures usually given as the lower limits of normal for the plasma level of vitamin A are probably high; that fair and adequate storage occurs with lower levels; that satisfactory adjustment at such levels can and does occur; and that a revision of so-called normal values for plasma vitamin A is indicated. Such a revision would be much more in keeping with the clinical rarity of frank vitamin A deficiency in adults, pregnant or otherwise. While no one would deny the need for an ade-

quate dietary intake throughout pregnancy, it would seem from the results of our study that most estimates of the vitamin A requirements of pregnant women are quite high, and that the administration of vitamin A supplements is unnecessary in ordinary instances.

The question of the importance of *optimal* as opposed to *adequate* dietary intake is not easily answered. Certainly, the administration of fat-soluble vitamins in ordinary therapeutic doses will do no harm.

Total Plasma Lipids

The blood lipids are almost always found to be increased in pregnant women, the increase usually beginning during the first trimester of pregnancy and continuing in the first weeks after delivery. The degree of hyperlipemia is unrelated to the nutritional state of the individual; this condition is known to occur after complete fasting, or in persons on restricted diets, where the inadequate supply of carbohydrates and proteins results in an increased demand for fat as fuel.

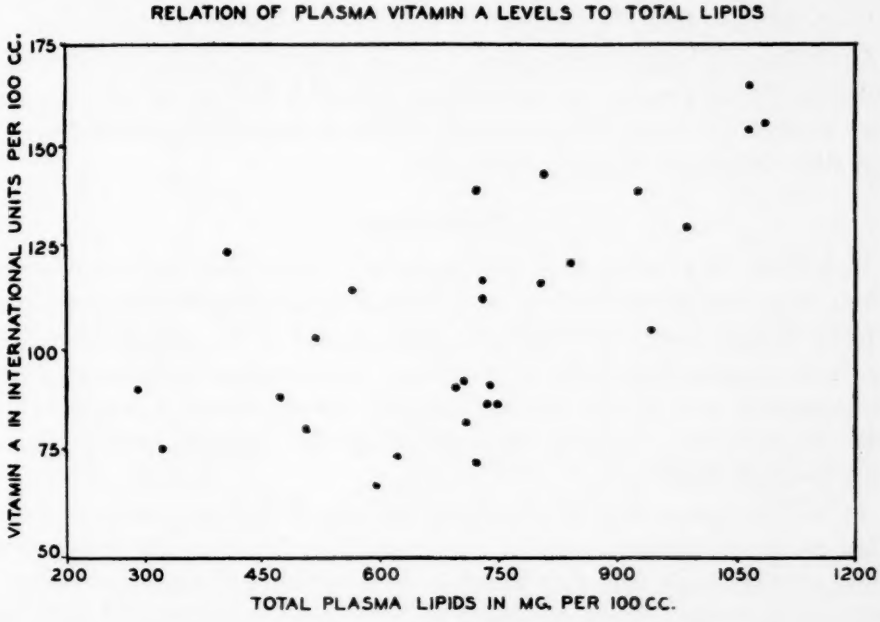

Fig. 1.

In the patients observed in this study a relationship between the plasma levels of vitamin A and the total serum lipids was noted (Table I). In general, patients with high values for total plasma lipids also had high vitamin A levels. The lowest plasma levels of vitamin A were found in those patients having the lowest lipid levels. In no individual patient was a high level of vitamin A found with a definitely lowered total plasma lipid content, or *vice versa*. The correlation is even more striking when it is realized that the concentration of plasma lipids may show considerable variation in normal individuals.

When the mean vitamin A level of all those patients having total lipids below 500 mg. per 100 c.c. is compared with the mean vitamin A level of all those patients with total lipids over 900 Gm. per 100 c.c., the difference is statistically significant. The mean vitamin A level for the first group is 82 international units, and for the second 134 international units.

It is possible that the plasma levels of both lipids and vitamin A are dependent on the degree of liver function and mobilization. The low plasma levels of total lipid and vitamin A found during acute infectious diseases could be explained on this basis. Thorbjarsen and Drummond have shown that greater amounts of vitamin A are stored in the liver when the fat content of the liver is increased, and that the administration of choline results in a diminution in the amount of liver fat as well as in the stores of vitamin A.[12]

It would appear that when the plasma lipids begin to rise during pregnancy as a result of increased fetal demands or as a preparation for lactation, a concomitant increase in the plasma levels of vitamin A occurs. Since this increase could not take place in the absence of adequate body stores and intake, the vitamin levels in the plasma represent the nutritional state of the individual. The broad relationship between the concentrations of total lipid and of vitamin A in the plasma during pregnancy and the puerperium is in keeping with the experimental work which suggests that the plasma lipids serve as a vehicle for vitamin A and allow its accumulation in the blood.

Conclusions

In a study of a group of gravid patients in the middle and upper economic brackets who were not maintained on special diets or given vitamin supplements, the mean plasma levels of vitamin A were found to be within normal limits throughout pregnancy and the puerperium. There was no evidence of a vitamin A deficiency in any of the persons studied, nor anything to suggest that the course of pregnancy or labor was altered in the patients having the lowest plasma level of vitamin A.

It would appear that the levels of vitamin A in the plasma are directly related to the nutritional state of the individual, but that the range accepted as normal is too high, and that satisfactory nutrition and storage do occur with lower plasma levels. There appeared to be no need for vitamin A supplements in the patients studied.

Studies of the total plasma lipids showed the development of hyperlipemia during pregnancy, the highest levels occurring during the puerperium. The patients with the most marked hyperlipemia also showed the highest plasma levels of vitamin A. When the patients with the highest and lowest total lipid values were separated into two groups, the difference between the mean vitamin A levels of the two groups was found to be statistically significant. This finding supports the experimental work suggesting that the plasma lipids may serve as a vehicle for vitamin A.

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A FURTHER DESCRIPTION OF A SET OF QUADRIOVULAR QUADRUPLETS

(A Study of Dermal Configurations and Tooth Eruption)

NORMA FORD WALKER, PH.D., TORONTO, CANADA

RECENTLY in this JOURNAL a quadruplet pregnancy was described by Dr. B. P. Watson,[1] and through the kind cooperation of the parents of the quadruplets, the writer was permitted to continue the study of the children. A comparison of the dermal patterns of their palms and soles has now been made, which study confirms the findings of Dr. Watson that the children are entirely a fraternal set, having arisen from four fertilized ova. The parents further cooperated during the first year by keeping records of the time of eruption of the children's deciduous teeth, and these data also give evidence of the quadriovular origin of the set.

Cases of quadruplet births in the United States from 1915 to 1942 (in each of which there was at least one live birth) number only 109, giving a proportion of one set of quadruplets in 490,699 confinements.[2] From 1920 to 1942 the proportion of the sexes in 99 cases was 209 females to 187 males, or 112 females to every 100 males. This ratio is considerably lower than the figure quoted by Watson from the *Statistical Bulletin of the Metropolitan Life Insurance Company*.[3] In the latter publication the data used were based on a period of only nine years, from 1933 to 1941, during which time the ratio was 156 females to 100 males. But during these years there happened to be large numbers of females born in each of three years. Over the longer period of twenty-three years, the proportion of females is much lower, being as stated above only 112 females to 100 males. When to the data from the United States there are added 17 more cases from Canada, New Zealand, Australia, South Africa, England, and Wales, the ratio is further reduced to 109 females to 100 males.[4-8] However, the trends pointed out by the Metropolitan Life can still be seen, namely, that the sex ratio of females to males increases in the multiple sets from twins to quadruplets. The number of females per 100 males is 94 in single births, 97 in twins, 101 in triplets and 109 in quadruplets. One would expect in quintuplet sets that the females would again be in the majority, and it may be due to the paucity of data that in the 46 recorded cases in which the sex of all infants is given the ratio is only 85.5 females to 100 males.[9-14]

In the 99 sets of quadruplets recorded in the United States census from 1920 to 1942, there were only 71 sets in which all four infants were born alive. Moreover, in the majority of these sets one or more infants died shortly after birth, so that comparatively few sets of quadruplets are later available for study.

A set of quadruplets may have its origin in one, two, three, or four ova, and each type has its special interest from the standpoint of heredity. Members of an uniovular set have a common heredity, since what was intended to be one individual has given rise to four individuals. In the four-egg set there is

no common heredity. The present biological study is concerned with the general problem of establishing the zygosity of such multiple sets from the analysis of dermal patterns. These patterns are particularly valuable because of their complexity and the fact that they are inherited, and also the ease with which they can be recorded and studied.

Until recently many investigators have held the opinion that the structure of the placenta was definitely indicative of the zygosity, but it is now known that uniovular twins may have a dichorionic placenta.[15, 16] Therefore, the number of choria does not necessarily correspond to the number of ova. The writer has under observation several pairs of identical twins whose dichorionic placentas are stored at the university. In the case of the Zarief quadruplets, here described, it happened that there were four choria corresponding to the four zygotes,[1] but the set might have originated from four, three, two, or one zygotes and still have had four choria.

The Zarief Quadruplets

The Zarief quadruplets were born in New York City on March 29, 1944. They included three girls and a boy. They were palm and sole printed when nine months old. Finger and toe patterns were not taken, since in young infants their small prints are time consuming to make, and in this particular study they had no special value.

The palmar patterns of the quadruplets are illustrated in Fig. 1 and formulated in Table I according to standard methods.[17] The recording of the position of the axial triradii by actual measurement (as suggested by L. S. Penrose) is, however, an innovation. To obtain this position the axis of the palm is measured first from the distal wrist crease to the proximal crease at

TABLE I. PALMAR FORMULAS OF THE ZARIEF QUADRUPLETS

Isodora	Left	11	X	7	5′	----- t(13.5) -----	A^u	0	0	0(V)	0
	Right	11	7	7	5′	---- t′(30.6) ----	L^r/V	0	0	0	1
Ellen	Left	11(10)	9	7(6)	5′	----- t(13.6) -----	L^r	L/V	0	L	0
	Right	11	9(10)	7(8)	5′	----- t(11.2) -----	L^r	V/V	0	L	0
Elaine	Left	11	9	7	5′	- t′(16.3)t′(33.7) -	L^r/L^u	0	0	L	V
	Right	11	9(10)	7(8)	3	---- t′(19.0) ----	A^u/A^c	0	0	L	0
Benjamin	Left	9	7	5′	3	---- t′(17.4) ----	L^r/A^c	0	M	0	1
	Right	10	9	7(6)	4	---- t′(27.5) ----	L^r/A^c	0	M	L	0

Symbols: A^u, arch ulnar; A^c, arch carpal; L^u, loop ulnar; L^r, loop radial; V, vestige; M, area of multiplication.

TABLE II. HOMOLATERAL DIFFERENCES IN THE MAIN LINES AND PALMAR PATTERNS OF THE ZARIEF QUADRUPLETS, COMPARED WITH THE MEAN DIFFERENCES FOR TWINS

SETS COMPARED	MAIN LINES AND AXIAL TRIRADII			PALMAR PATTERNS		
Zarief Quadruplets	Average Difference 23.5			Average Difference 42.9		
	Mean Diff.	S.D.	S.E.	Mean Diff.	S.D.	S.E.
Uniovular Twins	17.6	1.0	1.4	21.4	12.8	1.8
Binovular Twins	31 5	9.6	2.2	32.0	15.8	8.9

Abbreviations: standard deviation, S.D.; standard error, S.E.

the base of digit III; then the distance between the axial triradius and the distal wrist crease is taken, and the percentage of the latter in relation to the former is calculated. An axial triradius in any position from 0 to 14.9 is symbolized as *t*, from 15 to 39.9 as *t'*, 40 and over as *t''*. The palmar configurations of the quadruplets are then compared in pairs homolaterally, the average differences being given in Table II. From the latter table it will be seen that the

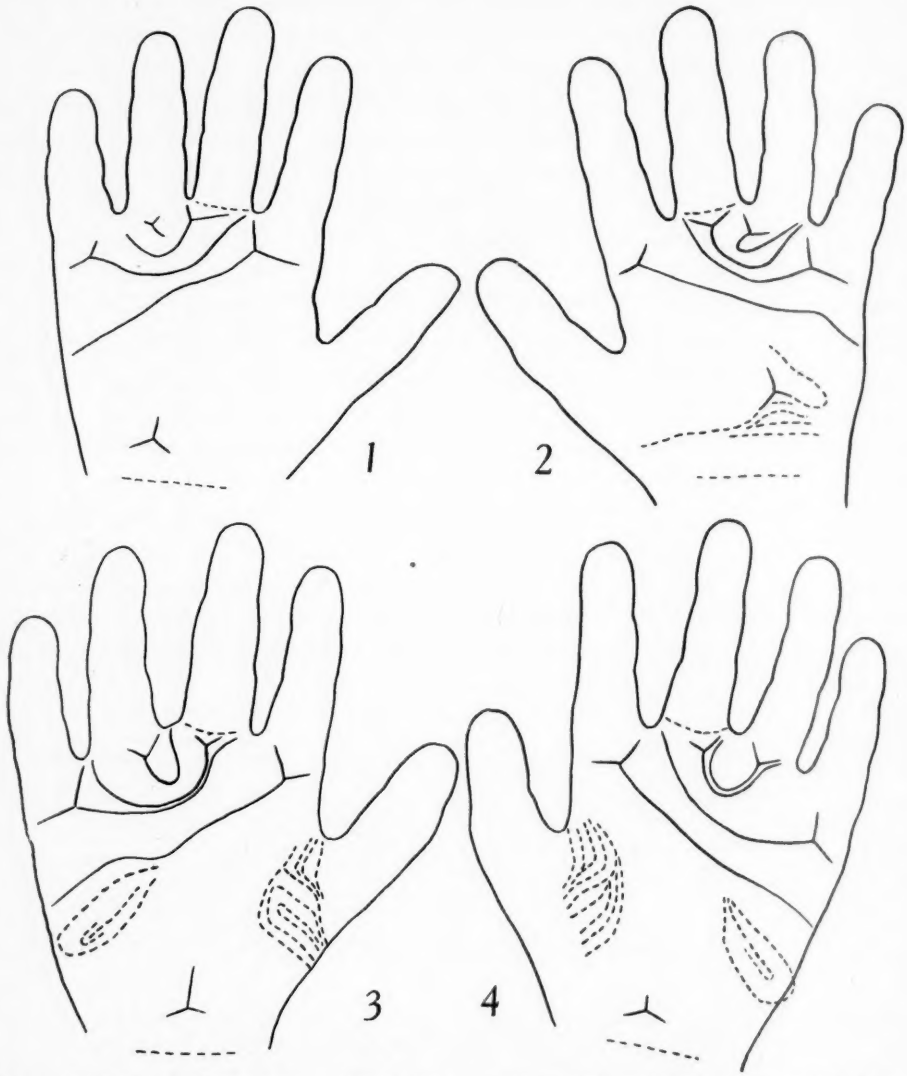

Fig. 14.—Outlines of the palmar configurations of the Zarief quadruplets. 1 and 2, left and right palms of Isodora; 3 and 4, of Ellen.

averages of these homolateral differences among the Zarief quadruplets are 23.5 per cent for the main lines and 42.9 per cent for the palmar patterns. Differences of this order are indicative of fraternal twinning.

An analysis of the plantar configurations of the Zarief quadruplets also confirms the diagnosis that they are a fraternal set. Outlines of the plantar

configurations are seen in Fig. 2 and formulated in Table III. The average homolateral difference amounts to 67.1 per cent for the main lines and 27.5 per cent for the plantar patterns.

Pattern of Eruption of the Deciduous Teeth.—Accurate records of the eruption of the deciduous teeth of the Zarief quadruplets were kept for the first year by the nurse in charge. The times of eruption are given in Table IV.

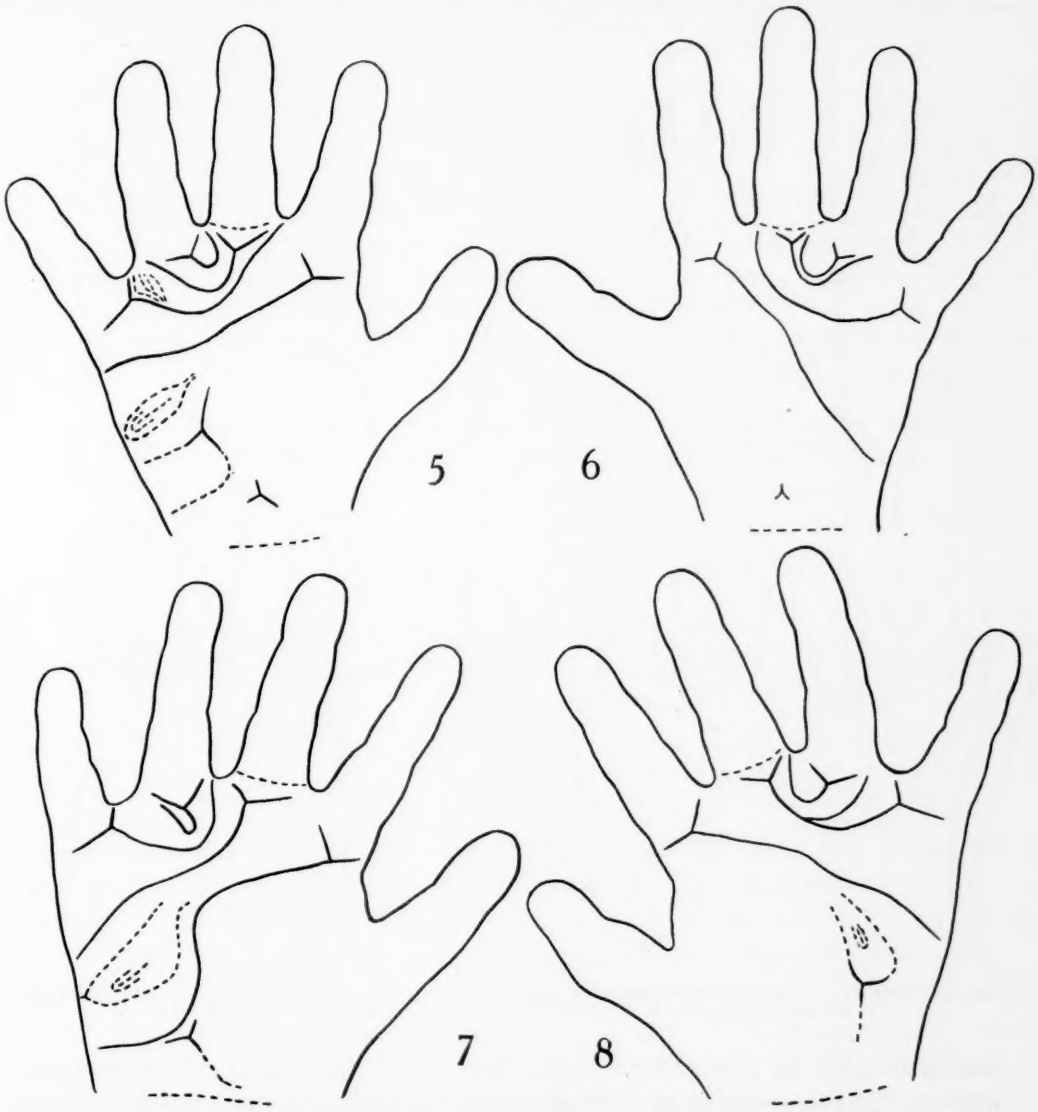

Fig. 1*B*.—Outline of the palmar congurations of the Zarief quadruplets. 5 and 6, left and right palms of Elaine; 7 and 8, of Benjamin.

It has previously been shown that the pattern of eruption of the permanent teeth is an inherited characteristic,[18] and it seems probable, therefore, that the same should be true for the deciduous dentition. To test this assumption, records of the time of eruption of the deciduous teeth of 64 pairs of twins have

TABLE III. PLANTAR FORMULAS OF THE ZARIEF QUADRUPLETS

Isodora	**Left**	15	9	7	15/7	13	0	0	0	$0/L^d$	0	L^d	0
	Right	15	0	9	15	13	0	0	0	$0/L^d$	0	L^d	0
Ellen	**Left**	15	11	9	7	7	0	0	0	$0/L^d$	0	L^d	0
	Right	14	9	7	7	6	0	0	0	$0/L^d$	0	L^d	0
Elaine	**Left**	15	15/11/9	X	15	15h	0	0	0	W/0	L^e	0	0
	Right	15	13/9	12	10	15h	0	0	0	W/0	L^d	L^d	0
Benjamin	**Left**	15	9	7	15	13	Lt.	0	0	$0/L^d$	0^v	L^d	0
	Right	15	10	8	7	13	0	0	0	$0/L^d_y$	0	L^d	0

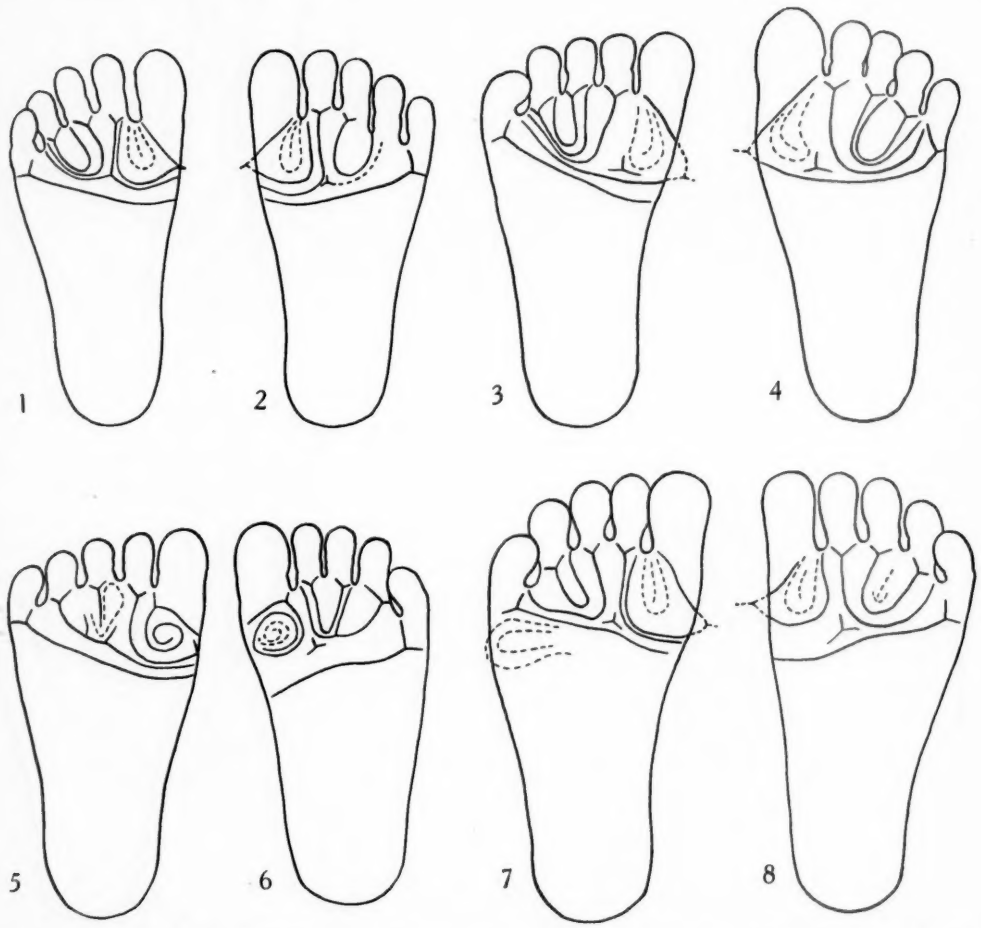

Fig. 2.—Outlines of the plantar configurations of the Zarief quadruplets. 1 and 2, left and right soles of Isodora; 3 and 4, of Ellen; 5 and 6, of Elaine; 7 and 8, of Benjamin.

been assembled by the writer. The differences in the timing of the eruption between the two members of uniovular and binovular sets are summarized and compared with those of the Zarief quadruplets in Table V. The quadruplets are again compared among themselves in pairs. It will be noted from the table that for each individual tooth the mean difference in time of eruption is smaller for sets of uniovular twins than for binovular twins, a result which confirms the assumption that the pattern of eruption of the deciduous teeth is inherited. It will also be noted that the average differences for the Zarief quadruplets are on the whole of an order indicative of a fraternal set.

TABLE IV. AGE IN DAYS AT TIME OF ERUPTION OF DECIDUOUS TEETH OF THE ZARIEF QUADRUPLETS

TOOTH	AGE IN DAYS OF ZARIEF QUADRUPLETS			
	ELAINE	ELLEN	BENJAMIN	ISODORA
Central Incisor				
Upper Rt.	246	291	245	337
Upper Lt.	264	293	263	340
Lower Rt.	208	242	209	263
Lower Lt.	231	247	216	264
Lateral Incisor				
Upper Rt.	354	341	270	
Upper Lt.	356	341	275	
Lower Rt.	338			
Lower Lt.	337			

TABLE V. SUMMARY OF DIFFERENCES IN TIME OF ERUPTION OF TEETH BETWEEN THE TWO MEMBERS OF UNIOVULAR AND BINOVULAR TWINS AND THE ZARIEF QUADRUPLETS (COMPARED AMONG THEMSELVES IN PAIRS)

TOOTH	UNIOVULAR TWINS		BINOVULAR TWINS		ZARIEF QUADRUPLETS	
	NO. OF SETS COMPARED	MEAN DIFFERENCE IN DAYS	NO. OF SETS COMPARED	MEAN DIFFERENCE IN DAYS	PAIRS COMPARED	AVERAGE DIFFERENCE IN DAYS
Central Incisor						
Upper Rt.	(19)	16.1	(40)	25.0	(6)	53.5
Upper Lt.	(20)	20.5	(39)	36.1	(6)	43.3
Lower Rt.	(20)	15.0	(44)	49.1	(6)	33.0
Lower Lt.	(19)	17.1	(44)	51.1	(6)	26.7
Lateral Incisor						
Upper Rt.	(16)	32.5	(33)	55.6	(3)	56.0
Upper Lt.	(18)	28.2	(33)	46.5	(3)	54.0
Lower Rt.	(15)	33.0	(22)	72.7		
Lower Lt.	(14)	15.1	(23)	86.7		

Summary

1. A comparative study of the dermal configurations of the palms and soles of the Zarief quadruplets confirms the earlier diagnosis that they are entirely a fraternal set.

2. Comparisons are here made with a new series of mean differences for the dermal configurations of uniovular and binovular twins.

3. Differences in the time of eruption of the teeth of the Zarief quadruplets are compared with new means for uniovular and binovular twins. The differences among the quadruplets confirm the diagnosis of their quadriovular origin.

4. A survey of 116 cases of quadruplet births gives a sex ratio of 109 females to every 100 males.

The writer wishes to thank Dr. Watson and also Miss H. M. Kelly, R.N., who arranged the necessary contacts for the study.

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A CLASSIFICATION OF OVARIAN TUMORS BASED UPON HISTOGENESIS

JOHN A. SPENCER, M.D., AND PHILIP J. REEL, M.D., COLUMBUS, OHIO
(From the Department of Obstetrics and Gynecology, College of Medicine, Ohio State University)

THE study of ovarian tumors has received a tremendous impetus of late years due to two main factors. First, the careful study, investigation, and reporting of a goodly number of the more unusual neoplasms, such as the masculinizing tumors and the group included in Novak's feminizing mesenchymomas, owing to their relative rarity and bizarre clinical picture. Fortunately for progress, however, the study of the rarer neoplasms has brought out facts which have shed a few rays of light on their less spectacular cousins. In so doing, the second major change has been wrought; the attempt to work out a truly scientific classification on a histogenetic basis.

Fischel's historic work on the embryology of the ovary, added to careful studies by Meyer, Schiller, MacCarty, Barzilai, and others, has given us a multiplicity of facts and theories which should result in a workable and practical histogenetic classification of ovarian tumors. The anatomicopathologic type of classification has been utilized by most pathologists to date, but from the broader standpoint of a grouping of tumors which may be more accurately divided and studied from the clinical standpoint, it seems to us that the histogenesis should shed additional light, particularly in regard to treatment and prognosis. Certainly, from the radiologic viewpoint, a more universal classification based on a histogenetic background would clear up the present very confused literature regarding the effect of deep therapy. It is still necessary to use descriptive terms to name different neoplasms properly, but it is no longer practical merely to classify these growths into cystic and solid and benign and malignant. In the absence of a universally accepted histogenetic classification, we wish to present a modification of the one suggested by Schiller. We realize that there are certain inadequacies, but hope that it may stimulate controversy and further thought.

We have divided all ovarian neoplasms into three broad classes:

I. Ovariogenetic: derived from ovarian tissue
II. Nonovariogenetic: derived from tissues foreign to the ovary, but found elsewhere
III. Carcinoma of Undeterminable Histogenesis

Following this basic structure and filling in the subdivisions lead to the following complete classification:

I. Ovariogenetic: (tumors developing from tissues of true ovarian structure)
  A. From the *mesenchymal core* of the ovary.
    1. From fetal cell remnants *without error in sex chromosomes*
      a. Granulosa cell tumors
      b. Theca cell tumors
    2. From fetal cell remnants *with error in sex chromosomes*
      a. Arrhenoblastoma—male
      b. Disgerminoma—neuter
    3. From interstitial tissues *without sex potential*
      a. Fibroma
      b. Angioma
      c. Myoma and fibromyoma
  B. From the *surface epithelium* of the ovary (prosoplasia toward the Müllerian duct)
    1. Serous cystoma (tube)
    2. Endometrioma (endometrium)
    3. Pseudomucinous cystoma (cervix)

II. Nonovariogenetic: (tumors developing from tissues not normally present in the ovary)
  A. By displacement into the ovary in fetal life
    1. Early—teratoma
      a. Mature—dermoid
      b. Immature—embryoma
    2. Late—tissue from structures contiguous to the ovary during embryological development
      a. Hypernephroma—adrenal
      b. Mesonephroma—kidney
      c. Brenner tumor—urogenital epithelium
      d. Ganglioneuroma—sympathetic ganglia
  B. By displacement into the ovary in adult life
    1. Metastases of malignant tumors—Krukenberg, etc.

III. Carcinoma of Undeterminable Histogenesis
  A. Carcinoma simplex, scirrhous carcinoma, plexiform carcinoma, etc.

Each of the listed benign tumors will have its corresponding malignant form, i.e., serous cystoma, serous cystadenocarcinoma, fibroma, sarcoma, etc. According to Schiller, "There has never been found a small beginning primary carcinoma of the ovary," as has been demonstrated so often in the cervix. On the other hand, it has been demonstrated in many instances that a carcinomatous overgrowth could be traced back to the superficial epithelium of the ovary, and cases have been observed in which tumor portions showing carcinomatous growth have been immediately adjacent to benign tumor growth of the same basic pattern. Therefore, it is felt that probably all malignant forms develop by secondary malignant transformation from a benign tumor.

Discussion of Tumors by Groups

I. **Ovariogenetic.—**

A. *From mesenchymal core:*

1. From fetal cell remnants *without error in sex chromosomes* (granulosa cell and theca cell tumors):

Histogenesis.—As shown by Fischel, the cells of the mesenchymal core differentiate to form granulosal (epithelial) and thecal (connective tissue) cells. These cells, in the normal process of cell division and growth, eventually mature into the fully formed wall of the normal follicle and normally secrete the female sex hormones estrin and progestin. Tumors developing from these elements, and secreting estrin and progestin, may be assumed to have developed by "normal" mitotic division of cells with no change, loss or error in their sex directing chromosomes. Thus, in differentiating the "feminizing mesenchymomas" from the arrhenoblastomas and disgerminomas—which are characterized by reversal or absence of normal female sex hormone production perhaps caused by some change, loss, or error in their sex-directing chromosomes —we have classed them as developing from the "sex-potential" cells of the mesenchyme without error in sex chromosomes.

Thecoma.—Schiller places the theca cell tumor with the fibroma and merely describes it as a luteinized form. However, it seems strange that a simple fibroma, ovarian or otherwise, should become luteinized. Certainly the usual nonspecific connective tissue of the ovary does not possess this potential anymore than does connective tissue any place else in the body. Hence, it seems to us that these "luteinized fibromas" must arise from the specific theca or protheca cell elements following some stimulus. It is thus a separate entity with a specific sex-hormone producing potential. Since the theca externa is principally fibrous tissue it is natural that varying degrees of fibroma-like development should be present, while from the lutein-potential cells the lutein areas will develop. In some of these tumors the fibroma element will predominate, while in more definite types the lutein, not luteinized, areas will be most evident.

Granulosa Cell Tumor.—According to Meyer, granulosa cell tumors arise from masses of unused and embryonic granulosa cells left behind in the medulla of the ovary. He states that these embryonic rests may be demonstrated in the ovaries of every full-term female fetus and that they have also been found in the ovaries of adults. Schiller feels that granulosal masses may arise, at any time, from mesenchymal cells whose inherent ability to form granulosal elements was not utilized in the embryo. Years later, due to an unspecified stimulus, these cells will exercise their inherent role. It may be that this "unspecified stimulus" is the unopposed action of the pituitary gonadotrops on the ovary. Schiller's statements are further substantiated by Barzilai and others who have noted that immature mesenchymal elements are found interspersed throughout both granulosal and stromal portions of the granulosa cell tumor. In either instance, these granulosal cell masses or embryonic potential granulosal cells represent a form of embryonic rest or cell remnant which may develop into a tumor at any time.

With the very close relationship, histogenetically, anatomically and functionally, between theca and granulosa cell elements it is not surprising that many thecomas contain granulosal elements and vice versa. von Haam[17] feels that the placement of these "mixed" types of tumors in one or the other category depends upon two facotrs: (1) the preponderance of one cell type over the other, and (2) the cell type which seems to be most actively proliferating. Novak had proposed the all inclusive term "feminizing mesenchymoma" to include granulosal and thecal tumors, both in their pure and mixed forms.

2. From fetal cell remnants *with error in sex chromosomes:*

The two tumors in this group, arrhenoblastoma and disgerminoma, are relatively rare but of extreme interest.

Histogenesis.—The arrhenoblastoma may, as described by Schiller, originate by an error in sex chromosomes during mitotic division of the "hormone-producing potential" cells of the ovarian mesenchyme; those same cells which,

in the normal ovary, produce the granulosa elements of the follicle. If these cells, during mitotic division, should lose an X-chromosome they would become male instead of female in character. They would, therefore, have the potency of the mesenchymal core of the testicle. Thus, they may give rise to a tumor which duplicates the fetal testicle, minus spermatagonia, but containing the male-hormone-producing Leydig cells. Meyer hypothesizes that the tumor originates in male-directed cells persisting in the hilus of the ovary from an early sexually ambivalent stage of gonadogenesis. Both Schiller and Meyer agree that the tumors arise from mesenchyme. Popoff and others have felt that these tumors are actually teratomas with an overgrowth of testicular tissue, and several authors have observed an admixture of teratomatous elements. However, as Meyer has pointed out, gonads are never found in a teratoma. We have classified this tumor as originating from a fetal cell remnant in the mesenchymal core of the ovary, but in contradistinction to the granulosa cell tumor developing with an error in sex chromosomes during mitotic division into an androgen-producing male-gonadlike tumor.

The neuter disgerminoma may also arise as the result of an error in sex chromosomes, an error of differentiation of the cells of the mesenchymal core of the developing ovary. Schiller feels that the mesenchymal cells thus may become sexually indifferent, developing in neither male nor female direction. Since this tumor is frequently found in association with some degree of hermaphroditism, and in both male and female, it would seem probable that there has been some degree of agenesis in the mesenchymal cells, some chromosomal malformation, some lack of stimulus to normal mitosis, and full development of their sexual function. Meyer, who first suggested the name, felt that they originated from "neutral disgerminal cells" found in the mesenchyme of the gonads before the stage of sexual differentiation. Others, such as Ewing and Meigs, felt that this tumor resulted from a one-sided development of a teratoma; Geist felt that they arose from certain cells of the surface epithelium of the anlage of the ovary.

3. From interstitial tissues *without sex potential:*

The fibroma and its malignant form, the sarcoma, make up the majority of tumors in this group. Other odd types such as the angioma, myoma and fibromyoma may be included although some authors deny the existence of the latter two.

Fibroma.—Coe and Geist designate this tumor as arising from the true stroma of the ovary, the musculofibrous tissue framework of the organ with its attendant vessels, nerves, and lymphatics. Fischel and Schiller state more specifically that it arises from the mesenchymatous core which normally furnishes the interstitial fibrous stroma. Schiller includes the thecoma as a subgroup of the fibroma, and for many years it has been designated as a xanthrofibroma. Since, however, the thecoma has definite hormonal activity—which has never been proved in the true fibroma—plus a typical histologic picture it has "come into its own." Hence, for these and other reasons previously noted, we have placed the thecoma with the granulosa cell tumor.

Sarcoma.—As in the case of other malignant ovarian neoplasms it is probable that most, if not all, sarcomas are derived by malignant transformation of a benign precursor. In Barzilai's study of approximately 10,000 ovarian specimens, she was able to find only three sarcomas which she felt were primary; other authors deny their existence. In the majority of instances a benign fibroma probably precedes the sarcoma, and cases have been recorded of this occurring according to Geist. In some instances an origin from the connective tissue of an embryonal teratoma may be possible, and some of the described chondrosarcomas, osteosarcomas, etc., have been felt by some to have this origin.

Angioma.—Novak describes this as being one of the "benign solid tumors, along with lymphangioma and neuroma, which may occur but is exceedingly rare." Geist states that it is usually a small discrete nodule in an otherwise normal ovary. Meyer and others have reported true cavernous angiomas.

Myoma and Fibromyoma.—The existence of these tumors has been questioned by some authors, but others have reported and described neoplasms containing fibrous and muscle tissue. Origin is from the smooth muscle tissue described in the ovarian core or from the smooth muscle of the blood vessels. The fibromyoma is much more frequent, and Geist quotes Basso as reporting forty-five cases in 1904. Aside from their rarity they behave, generally appear, and are treated like a fibroma.

B. *From surface Epithelium:*

In this group is included the serous cystoma, endometrioma, pseudomucinous cystoma and their malignant forms.

Histogenesis.—The surface epithelium of the ovary (previously designated as the germinal epithelium) originates from the primitive celomic (peritoneal) epithelium and, therefore, has the same origin as the epithelium which forms the Müllerian duct. This surface epithelium frequently invaginates into the cortex and may become pinched off to form the so-called Walthard cysts. These cysts are lined by cells which probably possess the same potentialities as Müllerian duct epithelium. Therefore, the surface epithelium (or the remnants of undifferentiated celomic cells found therein) may develop into a neoplasm with Müllerian characteristics by prosoplasia or metaplasia, according to Schiller. MacCarty has found that the lining epithelium of serous cystomas is occasionally continuous with the surface epithelium. He has also noted that in the contralateral grossly normal ovary there are often found indentations of the superficial epithelium in the form of microcysts and miniature papillomatous growths. According to Barzilai, these same indentations and microcysts may show typical tubal epithelial characteristics. She has thus proposed the name endosalpingioma for the serous cystadenoma with its characteristic high columnar, often ciliated epithelium.

Schiller goes even further and states that since the Müllerian potential of the surface epithelium is so marked, it is reasonable to assume that not only may the cells form neoplasms resembling the epithelium of the Müllerian-derived tube, but also neoplasms resembling the epithelium of the Müllerian-derived uterine cavity and the Müllerian-derived cervix. Thus the endometrioma, duplicating the histologic picture of the endometrium (but not to be confused with the endometriosis of Sampson), and the pseudomucinous cystoma whose tall, pale, mucinous secreting epithelium so closely resembles that of the cervix.

As both Schiller and Barzilai point out, it is not possible to place all pseudomucinous cystomas in the same histogenetic group. Probably there is some relationship, in certain cases, with Brenner cell nests. Barzilai states that some pseudomucinous cystomas originate from Brenner cell nests, and Dockerty states that about 30 per cent of Brenner cell tumors occur in the walls of mucinous cysts. Danforth states that in his study of fifty benign pseudomucinous cystomas no Brenner tumors were found, but that there is present in these neoplasms a basic nuclear type characterized by the presence of a median groove or fold. This nuclear detail is also present in the Walthard rests and Brenner tumors, and may be considered a point in the histogenesis of pseudomucinous cystadenomas. Other pseudomucinous cystomas have been observed deriving from the bowel epithelium of an adult teratoma. Schiller feels that those mucinous cystomas derived from other than surface epithelium may, with increasing knowledge, be eventually shown to be clinically different

and thus definitely indicate, by their clinical characteristics, the difference in their histogenetic background. It is probable that the great majority of these tumors arise from the surface epithelium; it is, as yet, impossible to differentiate those derived from other sources except in very exceptional instances.

Endometrioma.—In accord with the present trend of thought, we feel that it is necessary to utilize both Sampson's implantation theory and the theory of abnormal differentiation from celomic epithelium in order to explain entirely the occurrence of various forms of endometriosis. Certainly Sampson's theory has had the majority of adherents for many years, but Sampson himself modified his all-inclusive views of late. In order to utilize a comprehensive and logical classification we have held to the prosoplasis theory in explanation of the occurrence of the relatively rare endometrioma, as defined by Schiller.

II. **Nonovariogenetic.—**

A. *By Displacement Into the Ovary in Fetal Life:*

1. *Early*—Teratoma: *Mature*—dermoid, *Immature*—embryoma.

Histogenesis.—Multipotent cells, blastomeres displaced into the ovary in fetal life are described by Schiller as the origin of this group of tumors. Others have suggested the theory of parthogenetic development from an ovum; Barzilai feels that this latter theory will best explain the rare chorio-epitheliomatous tumor of the ovary. Most authors feel that origin from a somatic blastomere is the most logical theory so far put forth, although no completely satisfactory histogenetic background has as yet been proved. The term teratoma is the logical one and will cover the whole category. There has been, and still is, considerable confusion in the literature regarding terminology and the term teratoma is frequently misused to denote, of itself, malignancy. The adult teratoma exhibits relatively well-developed structures and a low grade of malignancy, as exemplified by the dermoid in which ectodermal elements predominate, although most of them contain cells of all three layers whose tissues are fully differentiated and tend to form organs. Less well-developed (immature) teratomas, whose potential is less definite, remain relatively embryonic in cell form and proliferative ability. These embryomas thus possess a high degree of malignancy.

2. *Late:* Tissues from structures contiguous during embryological development. (Hypernephroma, mesonephroma, Brenner tumor, ganglioneuroma):

Histogenesis.—Schiller's theory of the histogenesis of this group of tumors is accepted by most authorities, in general principle at least. The ovarian pedicle develops comparatively late, and therefore the ovary remains in close connection with other "regional" tissues for a long period of time. Finally, with the formation of two grooves or folds enclosing the ovarian ligament, it separates from the surrounding tissue. This separation occurs at a time in embryonic life when the cells have already become definitely differentiated. If these folds cut too deeply or are spaced wider apart than normal, non-ovarian tissues may be included. Schiller states that the hilum of the ovary often contains islands of adrenal cortical tissue much more frequently in the newborn than in the adult. Persistence of these inclusions and their neoplastic change give origin to the hypernephroma. Experimental work by Groat, Geist, and Gaines, etc., showed, after bilateral adrenalectomy, a proliferation of cells resembling those of the adrenal cortex present in the ovaries of animals that survived. Groat suggests a metaplasia from ovarian mesenchyme, but others feel this represents a growth of adrenal cell rests.

Schiller, who described the mesonephroma in 1939, explains the origin of this tumor from the inclusion of adjacent mesonephromatous tissue in the same manner as described above.

The inclusion of pinched-off elements of the immediately adjacent urinary system may give rise to the characteristic islands of transitional squamous epithelium of the Brenner tumor. Schiller and others, according to Barzilai, have actually observed transition from the rete ovarii to the Brenner epithelium. The relationship between Brenner tumor and the mucinous cystoma has been mentioned previously in this paper. Many authors (Novak, Meyer, Barzilai) feel this indicates that the mucinous portion is derived from the Brenner elements, while others (Dockerty and MacCarty) have thus postulated a teratomatous origin for the Brenner tumors associated with mucinous elements. Danforth postulates a possible origin of the Brenner tumor from Walthard cysts based on his observation of a common intrinsic architecture and nuclear detail. He considers the possibility that a small proportion of pseudomucinous cystomas may arise from Brenner cell rests.

Again, according to Schiller, when elements of the neighboring sympathetic ganglia are pinched off and included in the ovarian pedicle, a ganglioneuroma may develop.

B. *By Displacement Into the Ovary in Adult Life:*

1. *Metastatic* or secondary tumors of the ovary:

Histogenesis.—The ovary is a favored site of metastatic involvement arising mainly from two groups of organs; most frequently from the immediately adjacent pelvic organs and less frequently from the more distant gastrointestinal tract. Occasionally primaries are in the very distant organs such as the breast.

The much maligned Krukenberg tumor is the classic example in this group. In general the presence of signet-ring cells is pathognomonic, but other grossly typical metastatic forms may show a very high percentage of glandular formation. In the debatable cases it seems to be a play on words with various authors each forming rules as to exactly what constitutes a Krukenberg tumor. Actually we doubt if Krukenberg (or Marchand, who actually first described these tumors) would himself be as specific or rigid in his own interpretation. It is generally considered that the term indicates bilateral ovarian tumors arising from the mucous membrane of the abdominal cavity. Grossly they are demonstrated by large, solid, lobulated tumors usually preserving the outline of the normal ovary and histologically showing signet-ring cells in a fibromyxomatous stroma. Some investigators have added additional criteria, such as the absence of glandular formation, thus ruling out cases which would otherwise have been included. For this reason the number of true cases varies in different series from 153 to over 300.

The question of the pathogenesis of ovarian involvement has never been satisfactorily explained. Of the present three theories, peritoneal sedimentation, lymphatic spread and blood stream metastases, each has something in its favor and each has its proponents. The peritoneal sedimentation hypothesis probably is the one most generally accepted.

III. **Carcinoma of Undeterminable Histogenesis.—**

Histogenesis.—As mentioned previously in this paper, Schiller presents evidence that all ovarian malignancies, either sarcoma or carcinoma, are secondary in that they develop by malignant degeneration of a benign neoplasm; that they never arise as a primary malignancy. In the majority of instances there is sufficient evidence histologically to identify the carcinoma or sarcoma with its preceding benign form, as in a serous papillary cystadenocarcinoma. At times, with far-advanced growth, dedifferentiation has gone too far to allow us to trace the malignant form back to its parent benign growth. Therefore, with these tumors, we are forced to use purely descriptive terms such as carcinoma simplex, scirrhous carcinoma, etc. Novak particularly stresses our

utter ignorance of the histogenesis of these forms. Their known extreme degree of malignancy is, we feel, an attribute of their advanced stage rather than of a particular type of neoplasm.

Summary and Conclusion

1. A modification of Schiller's classification of ovarian tumors is presented, along with a discussion of the histogenesis of these neoplasms.

2. It is felt that a clear histogenetic concept is essential for diagnosis, treatment and evaluation of prognosis in the study of ovarian tumors.

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GRANULOSA CELL TUMOR

With a Presentation of Five Cases, One With an Associated Seven Months' Pregnancy

JOHN A. SPENCER, M.D., SAN FRANCISCO, CALIF., AND
ZEPH J. R. HOLLENBECK, M.D., COLUMBUS, OHIO

(From the Department of Obstetrics and Gynecology Ohio State University College of Medicine)

THE historical, histologic, and clinical aspects of granulosa cell tumor have been discussed in detail by many authors.[1, 2, 8, 12, 13, 15, 23] This tumor is reported to represent about 4 per cent of ovarian neoplasms,[18] although in general, and in a recent review of our own,[31] 2.5 per cent seems to represent a more accurate figure.

Histogenetically the granulosa cell tumor arises from mesenchyme; either from granulosa cell rests in the medullary portion of the ovary as held by R. Meyer,[1] or by development from unused, undifferentiated pro-granulosal elements of the mesenchyme as postulated by Schillar.[16]

The histologic pattern of granulosa cell tumors has been presented and discussed by many.[1, 12, 13, 15, 20, 21, 28] The picture is confused only in advanced malignant forms, where, as Schiller[16] points out, the anaplasia may obscure the resemblance to normal granulosa cells. Conversely, other tumors definitely not of granulosa cell type may present certain areas suggestive of such an origin.

Endocrine studies have been, in general, sparse and incomplete.[2, 4, 7] This has largely been due to the failure to recognize the syndrome preoperatively. Studies made have shown the presence of large amounts of estrin in the urine.[4, 5, 8, 10] Neuman, quoted by Schulze,[2] reported increased blood estrin. Geist and Spielman,[27] Klaften,[19] Gospe,[7] Palmer,[4] and others have demonstrated the presence of increased amounts of estrin in the tumor tissue.

In view of the known pituitary depressant action of large amounts of estrin, one would not expect to be able to demonstrate gonadotropic hormone in the presence of the granulosa cell tumor. This has not been, however, a persistent finding.[2, 4, 6, 10, 21, 24, 29] However, in some of Zondek's work[26] he noted that tremendous doses of estrin could be administered to amenorrheic women without lowering the excretion of Prolan A. It is interesting that the demonstration of gonadotropic hormone, by the A-Z test, has been noted principally in postoperative recurrences.[9, 10]

Our knowledge of the status of pituitary function in the presence of granulosa cell tumor is apparently confused. There are four possible reasons for this: (1) The amount of circulating estrin is relatively low, as noted in patients whose vaginal bleeding is profuse.[4] (2) The pituitary has become refractory to the depressing effect of estrin. (3) As we have noted, endocrine assays have been too infrequently and incompletely carried out. (4) We must consider the

*The authors wish to express their appreciation to Dr. E. von Haam, who carried out the endocrine assays and reviewed the pathologic specimens.

bizarre endocrine findings in, for instance, the normal menopausal individual, both from a clinical and laboratory standpoint. These are undoubtedly due to the variations in the regression-egression phase of ovarian-pituitary-adrenal relationship; the titer will depend upon the point in this phase during which the particular study is made.

Ninety per cent of these neoplasms are unilateral and may be partially or completely cystic. Estimates of malignancy vary from 10 per cent[1] to 28 per cent,[22] and late recurrences, up to nineteen years,[14] may occur. Conservative surgery is indicated in restricted growths, while radical extirpation plus roentgen therapy is utilized when extension is present.

Report of Cases

We wish to report, and briefly discuss, five patients with granulosa cell tumor. These represent 2.4 per cent of the ovarian neoplasms encountered on the gynecologic service of the University Hospital in the past fifteen years. The age grouping is fairly typical: 14, 40, 60, 66, and 74 years. Three were postmenopausal, and the remaining two were at the two extremes of active sexual life. Complete hormone studies were carried out in only one patient. One patient presented an associated pregnancy at seven months.

CASE 1.—The patient was a 74-year-old woman whose menopause had occurred at 41 years of age 32 years before. There was no further vaginal bleeding until two months prior to entry. At that time she experienced an episode of heavy vaginal bleeding which lasted for one week. Following this she had recurrent vaginal bleeding at two- to three-week intervals. For the ten to fourteen days prior to entry she had had a more or less constant scanty flow.

The past history was essentially negative. Her periods had begun at 13 years of age, were regular at twenty-eight days, and lasted four to six days. She had had five pregnancies and four full-term deliveries. There had been nocturia for ten years with occasional dysuria. Urgency during the few weeks before entry had been marked. There had been no weight loss.

The general physical examination was essentially negative and as expected for a woman of her age. There had been no breast changes. Pelvic examination showed a relaxed outlet; the vaginal mucosa showed clinical evidence of trichomonas vaginalis vaginitis, the mucosa was red and not the velvety smoothness of a typical senile mucous membrane. The cervix was grossly normal, with an old transverse laceration. The uterus was the size of a normal adult functioning organ, freely movable and regular in outline. The adnexa presented, on the right side, an eight centimeter, firm, freely movable, nontender ovarian mass.

The initial laboratory data showed a normal white blood count, slightly decreased red blood count and hemoglobin, and a slightly elevated sedimentation rate. The PSP was 35 per cent in two hours, but the BUN was 13.2, and the urine was negative. The Wassermann reaction was negative, and the electrocardiogram was suggestive of hypertensive heart disease. Pre- and postoperative endocrine data will be noted in the table.

On April 6, 1940, dilatation and curettage revealed a moderate amount of endometrium. At laparotomy, immediately following, the uterus was moderately enlarged, and presented a small median cleft representing a slight congenital malformation. The left ovary was about 1.5 cm. in diameter. The right ovary was solid, about 6 cm. in diameter, and appeared orange-colored beneath the capsule. The tumor was freely movable and the capsule was intact. A right salpingo-oophorectomy was done and the patient's postoperative course was uneventful, except that on the third postoperative day profuse vaginal bleeding

necessitated intrauterine packing. This bleeding persisted until the eighth postoperative day. The patient did not develop any of the typical vasomotor phenomena of the menopause postoperatively.

The pathologic report showed hyperplastic cystic endometrium and a granulosa cell tumor of the ovary. There was no microscopic evidence of malignancy.

This patient is alive and well with no evidence of her disease six years after her operation.

The pre- and postoperative laboratory data are as follows:*

	VAGINAL SMEAR	PROLAN	ESTRIN
3/11/40	Treated menopause	100 m.u./liter	150 m.u./liter
4/ 6/40	(Operation)	(Hyperplastic cystic endometrium)	
4/11/40	Menopausal		
4/14/40		Negative	Negative
4/15/40		Negative	Negative
4/16/40		10 m.u./liter	Negative
4/17/40		Negative	Negative
4/18/40	Menopausal	Negative	Negative
4/19/40		30 m.u./liter	Negative
4/22/40	Menopausal	(Endometrial biopsy—few glands, some still showing estrin stimulation; no cysts)	

Comment.—This case is typical in all respects, except that the patient falls into the upper age limit so far reported. Varangot,[21] in 266 cases, found only 12 over 70 years, and 74 years is the oldest we have been able to find reported in the literature. The presence of prolan preoperatively must indicate that the tumor was not forming sufficient estrin to entirely depress the pituitary. Why did the prolan disappear immediately postoperatively? Its appearance, eventually, would be expected in this postmenopausal patient. Others[25] have noted up to 25 m.u./liter of prolan in the urine on the eighth postoperative day.

Typical estrin withdrawal bleeding occurred on the third postoperative day. This has been noted by other observers.[5, 19, 24] Dworzak[20] reported a 52-year-old patient who passed an entire decidual cast on the sixth postoperative day. Probably, in our own case, if estrin bio-assay had been done immediately postoperatively, an almost immediate drop would have been noted, as has been reported by others.[4]

Preoperative diagnosis was made on the symptom complex: postmenopausal bleeding in a patient with a palpable ovarian tumor in whom the vaginal smear showed evidence of estrin stimulation, and in whom there was no evidence of fundal carcinoma, but a hyperplastic endometrium. Additional endocrine studies were done and proved confirmatory, but were not necessary for the diagnosis.

CASE 2.—A 40-year-old Negro woman, para vi, gravida viii, entered the hospital on the obstetric service on Jan. 25, 1941. Four hours after entry she spontaneously delivered a 3 pound, 8 ounce premature infant. Her last menstrual period was June 16, 1940, and her estimated date of confinement was March 23, 1941. She had made three visits to the prenatal clinic, two in December and one in January. For the two months preceding delivery she had had recurrent generalized abdominal pain and several attacks of nausea and vomiting. Immediately after delivery the abdomen remained distended and the patient continued to complain of pain. The possibility of multiple pregnancy was considered, but examination and a flat plate of the abdomen revealed the presence of a large intra-abdominal tumor. This was thought to be a mucinous cystoma of the right ovary, and the patient was transferred to the gynecologic service.

Inquiry into the patient's past history revealed the following significant points: menarche at 14 years of age with a regular 28-day flow lasting three to five days. Approximately one year prior to entry her periods had changed from a rather scanty three- to five-day flow to a profuse six- to ten-day flow, although the interval remained twenty-eight days. The pregnancy immediately preceding the present one resulted in a miscarriage at the fourth month and was accompanied by an unusually rapid enlargement of the abdomen. Earlier pregnancies had been term deliveries interspersed with miscarriages.

Laboratory tests showed a few white blood cells and numerous granular casts in the urine. Red blood cells were 4.53 million; hemoglobin, 14.5 Gm.; white blood cells were 23,250, with PMN 89 per cent. The BUN was 24, the sedimentation rate was markedly elevated, and the serology was negative. The temperature was 100° F., with a pulse of 96, while the blood pressure was normal. Physical examination was negative except for the presence of a symmetrical, midline, somewhat tender, firm partially movable abdominal mass extending from the pubis to 3 cm. above the umbilicus. Rectal examination revealed no abnormalities, and the mass did not extend into the cul-de-sac. Vaginal examination was not done because of the recent delivery.

On Feb. 5, 1941, laparotomy revealed about a pint of straw-colored, clear, free fluid in the peritoneal cavity. A large, semicystic tumor of the right ovary extended to the liver and was firmly attached to this organ, the transverse colon and the right iliac fossa. The lower pole of the tumor and the ovarian pedicle were free. The pedicle was clamped, incised, and suture-ligated. Adhesions were freed by blunt dissection and the tumor removed intact. Considerable brisk bleeding from the areas of adherence to the liver, colon, and iliac fossa necessitated the placing of two large gauze packs. The packs were removed fractionally over the next eight days, and the patient was discharged from the hospital on the fifteenth postoperative day. Two months after operation she was given a total of 4,000 Roentgen units to the pelvis.

The pathology report was as follows: "The specimen consists of a mass of tissue 22 by 17 by 11 cm. It is lobulated by cysts and lobules of tissue resembling fibroids. On cut section some cysts are loculated, others are large, single, and filled with a greenish-red viscid fluid. On cut section the tumor has a honeycombed appearance; many areas are the color and consistency of beef, and appear to be degenerating." Microscopically the tumor was a granulosa cell carcinoma.

This patient has been traced, and is alive and well five and one-half years after her operation.

Comment.—Schulze[2] states that "sterility is theoretically to be expected (in the presence of these tumors) through inhibition of the pituitary, and secondarily of the remaining ovary by the hyperestrinism produced by the tumor." She goes on to state that "association of granulosa cell tumors with pregnancy has been recorded twice in the literature, but as the details of neither case are available, it is difficult to evaluate them. One case is mentioned by Szathmary in which the tumor obstrucing labor at full term was removed, but he does not give the reference. Slamova, in 1937, records a case of granulosa cell tumor and simultaneous pregnancy in the *Czecho-Slovakian Gynecologic Journal* which is not available to me. Dockerty[12] states that "the presence of intrauterine pregnancy is very rare with granulosa cell tumor, but can occur with small neoplasms." Henderson,[11] reporting 21 granulosa cell tumors, stated that "The smallest tumor and the largest in the series were in this group of (six) neoplasms which failed to produce evidence (from clinical history and endometrial biopsy) of estrogen secretion. The smallest tumor was microscopic in size and was accidentally found in an ovary removed along with a pregnant uterus at the time of therapeutic abortion." There is no mention made as to the duration of

the pregnancy. Powell and Black[3] reported a case of coincidental pregnancy and an extra-ovarian granulosa cell tumor. This patient had had numerous abortions, and the tumor was discovered and removed three months after a five months' miscarriage. They make the interesting remark that this patient almost invariably menstruated, more or less regularly, throughout all of her pregnancies.

We have been unable to find, in the American literature, any other case of a third trimester pregnancy associated with a large granulosa cell tumor. It is probable that the tumor was present for at least a year before her delivery, as evidenced by the shift in her periods, and that it possibly caused her previous miscarriages. Why her last pregnancy went a full seven months is not clear. Unfortunately, the type of tumor was not suspected until too late, hence no endocrine studies were carried out. Their determination may have furnished a clue to the persistence of the pregnancy.

CASE 3.—A 60-year-old woman was admitted to the hospital on June 22, 1941, with a chief complaint of postmenopausal bleeding. Her last normal period had been twelve years before and there had been no further bleeding until fourteen days before entry. Painless vaginal bleeding had lasted for seven days, and for the seven days prior to entry there had been no bleeding or spotting. The past history was negative. Menarche occurred at 14 years of age, with a regular 28-day interval, and a four- to five-day flow. She had had two normal full-term deliveries. Her laboratory reports were essentially negative, as was her general physical examination. Pelvic examination revealed a somewhat succulent vaginal mucous membrane with a grossly normal cervix. The uterus was smooth, freely movable, and in normal position, but enlarged to about three times normal size. There was a 6 cm., rather firm, nontender, freely movable tumor of the right ovary. Endometrial biopsy, on June 23, showed hyperplastic cystic endometrium. Urinary estrin, on June 24, was reported as "over 100 m.u./liter."

A preoperative diagnosis of granulosa cell tumor of the right ovary was made and at operation, June 27, a nodular, partially cystic, freely movable, 8 cm. tumor of the ovary was removed. The left ovary was atrophic, and the uterus was about three times normal size. Pathologic examination confirmed the diagnosis of granulosa cell tumor of the ovary.

The patient was discharged from the hospital on the seventeenth hospital day after an uneventful convalescence. She did not develop postoperative estrin withdrawal bleeding, but on the eleventh day began to complain of typical "hot flushes." Follow-up, five years after operation, showed that this patient was alive and asymptomatic.

Comment.—This case is typical in almost all respects. A correct preoperative diagnosis was made on the basis of: postmenopausal bleeding, the presence of an adnexal tumor with an enlarged uterus, hyperplastic endometrium, and markedly increased urinary estrin. Further endocrine studies should have been carried out. Although estrin withdrawal bleeding was not noted, the physiologic response was evidenced by the occurrence of "hot flushes."

CASE 4.—A 14-year-old white girl entered the hospital on Sept. 14, 1945, with the chief complaint of abdominal swelling of three weeks' duration. The possibility of pregnancy was denied. Her present illness was apparently of gradual and asymptomatic onset, as the patient's sister first called her attention to the abdominal enlargement. For the two-week period prior to entry the patient had complained of occasional, fleeting, bilateral flank pain.

The past history was essentially negative. Menarche occurred at 12 years of age, with regular, five-day periods every twenty-eight to thirty days. Her last menstrual period was August 19, the preceding period July 20.

Laboratory tests were noncontributory, except for the following: flat plate of the abdomen showed no evidence of fetal skeleton, the Friedman test was negative. Pyelograms showed a dilated right ureter with some back pressure changes in the right kidney. The sedimentation was slightly increased.

Physical examination was normal except for the following: abdomen distended by a large, smooth, semicystic, nontender, movable mass which extended from the pubis to 4 cm. above the umbilicus. The size, shape, and consistency of this mass resembled that of a seven months' pregnancy. Pelvic examination showed a nulliparous outlet, a small cervix, with a slight brownish mucoid discharge from a grossly normal os. The uterus was not palpable, being pushed posteriorly by the abdominopelvic mass. Examination of the adnexal regions revealed that the same mass occupied the entire area on both sides. The patient's secondary sexual characteristics were entirely normal and well developed.

The preoperative diagnosis was merely ovarian cyst, probably right-sided. Unfortunately, none of the patient's symptoms suggested a granulosa cell tumor, and no endocrine analyses were made. At operation, on Sept. 24, 1945, the left ovary was completely occupied by a freely movable cyst with the tube stretched over the surface of the tumor. The uterus was small and in keeping with the patient's age. The right tube and ovary were grossly normal. The right ureter was markedly dilated in its pelvic portion. A left salpingo-oöphorectomy and appendectomy were done, and the patient was discharged on the thirteenth postoperative day after an uneventful convalescence. Examination one year later found her well and free from evidence of her disease.

The pathologic report was as follows: "The specimen was a large cystic mass measuring 22 by 17 by 12 cm. It weighed over 1,000 Gm. The outer wall was translucent in places, in others it was opaque. Veins were noted running beneath the surface. The cyst was filled with an amber-colored, thin, clear fluid. The cyst wall was thin, measuring no more than one to two millimeters, and in places less. The inner lining was smooth. Near one edge was a protuberance nine to ten centimeters in diameter and projecting into the main cyst. This protuberance was a solid, jelly-like mass well encapsulated and partially cystic." The microscopic examination, after special reticulum and fat stains, showed a tumor of granulosa and theca cells with luteinization. The proliferative elements were granulosa cells. The final diagnosis was a granulosa cell tumor, with an abundance of luteinized stroma.

Comment.—This patient, clinically, presented none of the typical symptoms of a granulosa cell tumor in spite of its size. With the presence of large amount of luteinized stroma, it is possible that the estrogenic effect was counterbalanced by a progestin effect. Novak[15] mentions several reported cases in which, with almost complete luteinization, the endometrium presented evidence of marked progestin effect. It is extremely unfortunate that neither an endometrial biopsy nor endocrine analyses were obtained in our case. The microscopic picture bears out Novak's feeling that most of these tumors are mixed types containing both granulosal and thecal elements.

CASE 5.—A 66-year-old white woman was admitted to the hospital with a chief complaint of swelling of the abdomen of about four months' duration. Six months prior to entry the patient noticed a "bearing down" sensation in the pelvis and stated that her "womb" would drop down when on her feet. About three months before entry she noted "lumps" in both inguinal regions and two weeks before entry her umbilicus became red and then purple and was very tender. She had lost about 23 pounds during the year prior to entry. Her past history was essentially negative. Menopause had occurred at 50 years of age and she had had no bleeding since.

Physical examination was negative except for the following: the abdomen was flat with a small, tender, purple, one centimeter mass in the umbilicus. There was a small, tender, firm, somewhat movable mass in the lower left quadrant. There were bilateral, discrete, tender, enlarged, inguinal nodes. Pelvic examination showed a small uterus with a firm, somewhat movable, irregular, nontender, 10 cm. left adnexal mass. The laboratory examinations were entirely normal except for evidence of a secondary anemia. No endocrine studies were carried out, as the type of tumor was not suspected.

At operation a left-sided ovarian tumor was found with invasion locally and throughout the lower abdomen. The gross mass was removed, and the patient given postoperative roentgen-ray therapy.

The pathologic report was as follows: "The specimen weighed 550 Gm. On one side there were large, soft, mushy nodules, some of which were thin walled and contained fluid. The other side of the tumor consisted of very friable, grossly malignant tissue." Microscopically the slides showed small round and spindle cell types with a peritheliomatous arrangement, highly anaplastic." Diagnosis was "granulosa cell carcinoma of the ovary."

We have been unable to trace this patient, but her clinical picture practically precludes a long life.

Comment.—This case is not typical of the granulosa cell tumor as a group. The absence of vaginal bleeding, and other signs of "rejuvenation" gave no clues and hence no endocrine studies were made. Apparently the hormonal effect of the tumor was not pronounced. Fauvet[17] mentions a similar picture in one of his cases. Geist[30] states that there may be no bleeding in postmenopausal patients with granulosa cell tumor. It is interesting that neither of our two granulosa cell carcinomas presented evidence of really marked hormonal effect. Obviously, the amount of hormone produced by individual tumors may vary markedly. There has not, as yet, been sufficient work done to correlate tumor type with the quantity of estrin production.

Summary and Conclusions

1. Five cases of granulosa cell tumor are reported and discussed.

2. These five cases represent 2.4 per cent of all ovarian neoplasms encountered on the gynecologic service of the University Hospital in the past fifteen years.

3. One of the five cases represents the first third trimester pregnancy associated with a large granulosa cell tumor reported in the American literature. Two questionable cases are noted in the foreign literature.

4. One case, only, was completely examined from an endocrinologic standpoint.

5. Two of the five cases were undoubtedly carcinomas, the remaining three exhibited no evidence of malignancy.

6. Age grouping was typical, although none were prepuberty.

7. In typical cases the preoperative diagnosis is self-evident and hormonal studies are obtained. In the absence of typical signs and symptoms endocrine studies are usually entirely lacking. Complete hormonal studies are still relatively rare in the general literature.

8. It is apparent, from our own work and reports in the literature, that gonadotropic endocrine assays are of no clinical significance in the diagnosis

of primary granulosa cell tumor. Increased urinary gonadotropic levels, as determined by the A-Z test, may be of some diagnostic value in recurrence of this tumor.

9. Only by carrying out routine and complete endocrine studies in all cases of ovarian tumor, regardless of symptomatology, will sufficient accurate data be accumulated to be of real diagnostic and prognostic value.

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MEPRANE: AN EFFECTIVE ESTROGEN FOR INHIBITION AND SUPPRESSION OF LACTATION

DONALD COULTON, M.D.,* BOSTON, MASS.

(From the Department of Obstetrics, Boston University School of Medicine, and the Massachusetts Memorial Hospitals)

SINCE 1938, when Dodds and his co-workers[1] presented stilbestrol as an effective estrogen for oral use, synthetic oral estrogens have been produced in ever-increasing number and variety. This development is partly explained by the need for a more effective and less toxic preparation. The inhibition and suppression of lactation by estrogens, although the mechanism is not yet clearly understood, is not only an extremely useful form of therapy, but also affords a rapid method of evaluating the effectiveness and acute toxicity of any new estrogen. Thus, an estrogen may be judged by the incidence of toxicity or side-effects, the effectiveness or certainty of inhibition and suppression of lactation, the speed of relief from symptoms afforded, and the duration of treatment required.

With the use of these standards of comparison, a new synthetic oral estrogen, meprane, has been studied in the following 183 cases.

Chemical Composition and Relative Potency

Meprane, 3, 4-bis (m-methyl-p-propionoxyphenyl) hexane, is a synthetically prepared estrogen intended only for oral use. Its relative estrogenic activity was determined by the method outlined in the *Memorandum of the International Standard for the Oestrus-Producing Hormone*,[2] utilizing the effect on vaginal smears of rats receiving the preparation both orally and parenterally. Compared with other estrogens, meprane when used orally was found to be one-half as active as stilbestrol and twelve times more active than estrone. Toxic effects from meprane were not encountered, even when five times the toxic dose of stilbestrol was given.[11]

Material and Methods

The following consecutive 183 cases include both ward and private patients of the Massachusetts Memorial Hospitals. Only those who were unable to nurse or in whom suppression of lactation was otherwise indicated were treated.

The aim of the project was twofold. First, the optimum course of treatment for inhibition or suppression of lactation was sought. This was done by varying the daily dosage, the frequency of administration, and the duration of treatment. Complaints were noted, and the condition of the breasts and axillae of each patient was observed daily until discharge. Second, a search for acute toxicity or untoward side-effects was made, special attention being given to gastrointestinal disturbances. Comparative laboratory studies intended to evaluate liver, renal, and hematopoietic functions were also done at the beginning and end of treatment.

Results were graded as excellent, satisfactory, fair, or failed. In those graded excellent, inhibition or suppression was complete without supplementary

*This investigation was sponsored by a grant from Reed and Carnrick, Jersey City, N. J.

treatment other than the application of ice bags to the breasts for twelve to twenty-four hours in occasional cases of unusually painful engorgement. The results were considered satisfactory if at the time of discharge suppression was complete except for minimal or slight leakage which ceased spontaneously within two days and required no specific therapy. The results were considered fair if breast leakage at the time of discharge was moderate or was associated with either breast tenderness or firmness, but ceased within the next few days at home without supplementary treatment other than ice bags applied to the breasts. Any transient recurrence of lactation was considered only a fair result, provided it ceased spontaneously within two to three days. Any case requiring supplementary treatment, either in the hospital or for recurrence after discharge, because of persistent leakage and engorgement, or both, would have been considered a failure, but no such case occurred.

Results

In an attempt to find the optimum method of treatment, seven different courses of therapy were carried out in order to establish the shortest possible course producing optimum results (Table I). Three of these (Courses I, II, and III) were considered inadequate and were discontinued. The shortest dura-

TABLE I. COURSES AND RESULTS

	COURSES													
	I		II		III		IV		V		VI		VII	
Total dosage	8 mg.		10 mg.		9 mg.		15 mg.		12 mg.		12 mg.		12 mg.	
No. of patients	12		7		14		10		52		57		31	
	RESULTS													
	I		II		III		IV		V		VI		VII	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Excellent	10	83.3	5	71.4	9	64.3	9	90.0	48	92.3	56	98.2	29	93.5
Satisfactory	2	16.7	0		4	28.6	1	10.0	3	5.8	1	1.8	2	6.5
Fair	0		2	28.6	1	7.1	0		1	1.9	0		0	
Failed	0		0		0		0		0		0		0	

Course I: 1 mg. twice daily for 4 days.
Course II: 1 mg. twice daily for 5 days.
Course III: 1 mg. thrice daily for 3 days.
Course IV: 1 mg. thrice daily for 5 days.
Course V: 1 mg. thrice daily for 4 days.
Course VI: 1 mg. four times daily for 3 days.
Course VII: 2 mg. twice daily for 3 days.

tion of therapy has been emphasized, since it allows the patient to be observed for possible recurrence after the discontinuance of treatment. Comparison of the separate courses indicates that a total dosage of 12 mg. must be given in order to obtain optimum results without regard to whether treatment was begun before or after the onset of lactation. Varying the frequency of medication or total duration of treatment within reasonable limits produced only minor variations in the final results. When less than 12 mg. was given, as in Courses I, II, and III, the results indicate inadequate treatment. These courses are therefore not included in the following statistics.

Excellent Results

Lactation.—It is of clinical significance to determine the most effective time to begin treatment. Walsh,[10] Douglas,[5] and others, using various oral estrogens, have reported greater success when treatment was not begun until after the

onset of lactation. The results of this series, however, show no consistent variation due to the influence of lactation. As seen in Table II, 94.3 per cent of the

TABLE II. RESULTS IN LACTATING AND NONLACTATING CASES

	RESULTS								
	EXCELLENT		SATISFACTORY		FAIR		FAILED		TOTALS
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER
Lactating	60	95.2	2	3.2	1	1.6	0		63
Nonlactating	82	94.3	4	4.6	1	1.1	0		87

87 cases receiving treatment before the onset of lactation had an excellent result, compared with 95.2 per cent of the 63 cases receiving it after lactation had begun.

This impression was con firmed by analyzing all cases receiving adequate therapy, according to the postpartum day on which treatment was initiated (Table III). Of the 17 cases in which it was begun on the first postpartum day,

TABLE III. INFLUENCE OF TIME TREATMENT WAS INITIATED

	RESULTS								
	EXCELLENT		SATISFACTORY		FAIR		FAILED		TOTALS
POSTPARTUM DAY	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER
1	14	82.4	2	11.8	1	5.8	0		17
2	56	98.2	1	1.8	0		0		57
3	36	92.3	2	5.1	1	2.6	0		39
Subsequent	36	97.3	1	2.7	0		0		37

only 82.4 per cent had excellent results. Apparently this was due to inadequate continuation of therapy after the third postpartum day, when the majority of patients showed some evidence of engorgement. However, treatment begun on the second postpartum day, before the onset of lactation, achieved the highest percentage of excellent results (98.2 per cent). The cases in which treatment was begun on the third and subsequent postpartum days, when lactation was almost invariably present, showed 92.3 and 97.3 per cent excellent results, respectively. Therefore, although treatment begun on the second postpartum day was slightly superior, no striking differences were noted between inhibition and suppression of lactation.

Moreover, it was the clinical impression that treatment begun not earlier than the second postpartum day gave uniformly optimum results. There was no appreciable difference in the duration of symptoms in patients beginning treatment before the onset of lactation compared with those beginning treatment after onset, the average duration of symptoms for all cases in both groups being 1.6 days and 1.4 days, respectively.

Parity.—Parity was seen to exert a moderate influence on results (Table IV). Without exception, all courses were more successful in primiparas than

TABLE IV. INFLUENCE OF PARITY ON EXCELLENT RESULTS

	COURSE									
	IV		V		VI		VII		TOTALS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Primiparas	4	100.0	23	100.0	28	100.0	11	100.0	66	100.0
Multiparas	6	83.3	29	86.2	29	96.6	20	90.0	84	89.3

in multiparas. This influence is strongly brought out when the results of all the adequate courses are combined; 100.0 per cent of primiparas produced excellent results, compared to only 89.3 per cent of multiparas.

The inferior results encountered were almost evenly distributed between lactating (3 cases) and nonlactating (5 cases), again indicating no appreciable influence due to this factor alone (Table V).

TABLE V. INFLUENCE OF PARITY AND LACTATION ON EXCELLENT RESULTS

	NUMBER	PER CENT
Primiparas:		
Lactating	28	100.0
Nonlactating	38	100.0
Multiparas:		
Lactating	35	91.4
Nonlactating	49	89.8

Age.—Age was also a definitely determining factor, since the older age group uniformly obtained better results from therapy regardless of parity, as shown by Table VI.

TABLE VI. INFLUENCE OF AGE ON EXCELLENT RESULTS

AGE	PRIMIPARAS		MULTIPARAS		TOTALS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
15-29 years	59	100.0	37	81.1	96	92.7
30 and over	7	100.0	39	97.4	46	97.8

Since multiparas were less satisfactorily dried up than primiparas, it might be expected that the older age group would show less satisfactory results. This, however, was not true, since both multiparas and primiparas showed better results in the older age group, the influence of multiparity being felt almost entirely in the younger multiparas. Beyond the age of 30 years, parity did not influence the results.

Therefore, in this series it is apparent that young multiparas were the most difficult to treat successfully, while the presence or absence of lactation had little or no influence.

Suboptimal Results

The results in 8 (5.3 per cent) of the 150 patients receiving adequate therapy were graded as nonexcellent. All these spontaneously dried up within two to three days after discharge, yielding a clinically satisfactory result. There were no failures of inhibition or suppression of lactation in any of the various courses of adequate treatment, and no patient required supplementary treatment for persistent or intense symptoms. No case of breast-caking occurred. Only one case of this group represented a recurrence of lactation, an incidence of 0.6 per cent for the entire series receiving adequate therapy. Analysis of the nonexcellent cases revealed that 62.5 per cent were entirely negative except for some degree of leaking; 12.5 per cent had only some degree of breast firmness, while 25 per cent had both leaking and firmness. No patient complained of breast tenderness (Table VII).

When the statistics are analyzed for influencing factors producing nonexcellent results, it is of interest to note that all the patients were multiparas. Also, most of these results were seen in patients under 30 years, three patients (37.5 per cent) being between 15 and 25 years old, 4 (50 per cent) between 25 and 30 years, and 1 (12.5 per cent) over 30 years. The presence or absence of lactation and the postpartum day on which treatment was initiated were not significant factors.

TABLE VII. ANALYSIS OF NONEXCELLENT RESULTS

CASE NO.	LACTATION	PARITY	AGE (YEARS)	SYMPTOMS
319621	Yes	M	35	Slight firmness
*320014	Yes	M	18	Slight leakage
321018	No	M	29	Slight leakage
322302	No	M	27	Moderate leakage
320971	No	M	25	Slight leakage
318378	Yes	M	28	Slight leakage
318924	No	M	24	Slight firmness; slight leakage (unilateral)
319550	No	M	23	Moderate firmness; moderate leakage

*Recurrence.

Thus, inspection of the suboptimal results confirms the findings in the excellent group; i.e., the less satisfactory results occurred entirely among multiparas, and chiefly in patients under 30 years of age.

Toxic Side Effects

Patients were examined daily to discover possible side effects, particular attention being paid to gastrointestinal disturbances in relation to therapy. Laboratory studies including urine analyses, hemoglobin, nonprotein nitrogen, and total protein determinations were also done at the beginning and end of treatment.

Clinically no evidence of toxicity occurred. This was supported by laboratory data, which remained unchanged except for effects attributable to recent labor and delivery. A rising hemoglobin and total protein with a falling nonprotein nitrogen were consistently noted, particularly in patients having sustained a long labor or an excessive blood loss at the time of delivery. Small amounts of sugar and albumin were usually noted in the urine, but were transient or had existed previous to therapy, no case showing a persistent increase in either. Thus, Meprane in dosages of 12 to 15 mg. given over a period of three to five days appears to be without acute toxic side effects.

Comparative Results

It is of interest to compare our findings with the use of Meprane for inhibition and suppression of lactation with those of other investigators who employed various oral estrogens for the same purpose. Due to the large volume of literature, only a few of the more recent and typical reports will be compared.

Stilbestrol is perhaps the commonest oral estrogen previously used. Fields[3] reported 150 cases in which treatment with stilbestrol was begun forty-eight hours after delivery before the onset of lactation; there were 5 per cent failures. Of an additional 150 patients, in whom treatment was begun after a short period of nursing, 14 per cent suffered either breast discomfort, engorgement, or leakage during treatment, and 2.6 per cent had leakage after discontinuance of treatment. Fields also found that in rare cases stilbestrol had no obvious effect on lactation. Barnes[4] reported 60 per cent successful results with stilbestrol, 41 per cent with dienestrol, and 38 per cent with hexestrol. In 23.5 per cent of all his cases lactation recurred, and in 2.2 per cent some toxic effects were exhibited.

Douglas and co-workers[5] using diethylstilbestrol, reported 33 per cent successful results when treatment was begun before lactation and 40 per cent when it was begun after the onset of lactation. Diddle and associates,[6] using diethylstilbestrol, reported 63 per cent good results, 25 per cent fair, and 12 per cent failures. With alpha-estradiol the percentages were 37, 38, and 23

per cent. Palmer and co-workers,[7] using diethylstilbestrol on 219 patients, found only 4 per cent failures when the optimum dosage of 5 mg. was given on the first, second, sixth, and seventh postpartum days.

Murphy,[8] using octofollin, 5 mg. three times daily for four days, had excellent results throughout a series of 20 cases including both lactating and nonlactating patients. Kurzrok et al.,[9] using ethinyl estradiol in various dosages, obtained from 65 to 94 per cent excellent results and 35 to 6 per cent poor results or failures.

In the present series when an adequate dosage of 12 mg. of meprane was used over a period of three to five days in 150 patients, the results were excellent in 94.7 per cent, satisfactory in 4.7 per cent, and fair in 0.6 per cent. No failures of inhibition or suppression of lactation occurred. No toxic effects were found either by examination of the patient or by laboratory studies done before and after treatment. Meprane is thus shown to be an effective and potent oral estrogen for inhibition or suppression of lactation, apparently without toxic or side effects.

Conclusions

Meprane, a new synthetic estrogen for oral use, has been given a clinical trial in the suppression and inhibition of lactation under carefully controlled conditions. Various dosages and courses of treatment were empirically used, on the basis of an estimate of potency determined by previous animal experimentation. Possible toxic side effects were carefully sought, by both examination and laboratory studies before and after treatment.

One hundred eighty-three patients were given one of seven different courses of therapy. Three courses were eliminated as inadequate. The results of the remaining four courses, including a total of 150 patients were analyzed. No other form of supplementary treatment except the occasional use of ice bags on the breasts for twelve to twenty-four hours was employed.

The optimum course of treatment, as determined by the speed of symptom relief, the certainty of inhibition or suppression, and the shortest possible duration of treatment, was 1 mg. four times daily for three days. The presence or absence of lactation at the time treatment was initiated exerted no influence on the results. The best results were obtained when this course was begun after the first postpartum day. Primiparas responded better than multiparas, and patients over 30 years of age better than younger ones. Patients remaining symptomatic at the time of hospital discharge quickly became asymptomatic, aided only by the application of bags to the breasts. Such symptoms in all cases were minor and transient. No case in any course presented any evidence of toxic side effects as determined by examination of the patient and confirmed by laboratory studies.

A comparison of meprane is made with other oral estrogens used for the suppression of lactation. From this preliminary study, meprane appears to be definitely superior in the percentage of excellent results, the short time over which treatment need be continued, and the complete lack of toxic side effects.

Summary

Meprane, a new synthetic estrogen for oral use, has been given a clinical trial.

Seven different schedules of dosage were given to a total of 183 consecutive cases. Three schedules were eliminated as inadequate. In the remaining four schedules, including 150 patients, the results were as follows: excellent, 142 patients (94.7 per cent); satisfactory, 7 patients (4.7 per cent); fair, 1 patient (0.6 per cent); failures, 0.

The optimum schedule of dosage was 1 mg. four times daily for three days. The results of this schedule were as follows: excellent, 56 patients (98.2 per cent); satisfactory, 1 patient (1.8 per cent); failures, 0.

The influence of lactation, parity, and age have been analyzed.

No toxic side-effects were noted.

A favorable comparison of meprane with other oral estrogens used for suppression of lactation is made.

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A CLINICAL STUDY OF A NEW SYNTHETIC ESTROGEN

HAZEL A. C. LIN, M.S., M.D., JERSEY CITY, N. J.
(From the Endocrine Clinic, Jersey City Medical Center)

AN ORALLY effective synthetic estrogen, 3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane* has been used during the past ten months in the Endocrine Clinic, Jersey City Medical Center, for the treatment of 43 menopausal patients in 71 courses, for two cases of premenstrual tension, one primary amenorrhea, one secondary amenorrhea, and one severe migraine. This report exclusively confines itself to the first group—menopausal patients.

Method of Investigation

3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane was administered to 43 patients in 71 courses. Subjectively, the effectiveness of the drug was noted by the relief of symptoms. Objectively, the vaginal smear method of Papanicolaou and Shorr was employed as an index. Endometrial biopsies were taken with Novak curette, and the vaginal Ph was determined by the use of nitrazine paper.

More detailed studies were carried on in several selected cases. Tests given were quantitative blood and urine estrogens, basal metabolic rate, blood cholesterol, nonprotein nitrogen and blood counts. A weekly record was kept of the patients' bodily weights.

Analysis of Results

Of the 43 menopausal patients treated, 18 were Negro and 25 were white. Menopause was spontaneous in 26 patients, and was of the artificial type in 17.

Symptoms

The symptoms were classified according to Sevringhaus,[1] and are recorded in Table I.

The only symptom which was unaffected by this therapy was arthralgia. Two patients complained of vague joint pains and stiffness. It was in these two patients also that the hot flashes were only slightly improved.

Patient F. R., aged 52 years, was first seen on March 21, 1946, for amenorrhea of nineteen months' duration. She began having hot flashes, sweating, melancholy, insomnia, and vague joint pains and stiffness six months prior to visiting our clinic. Vaginal smear was reaction II. She was given this estrogen 1 mg. three times a day for six weeks. Hot flashes, sweating, and Melancholy improved slightly, but the other symptoms remained unchanged, although her vaginal smear was in full reaction IV at the end of the therapy.

Patient R. A., aged 44 years, paid her first visit to our clinic on Feb. 28, 1946, with the chief complaint that of innumerable hot flashes, joint pain, fatigue, and insomnia. Her vaginal smear was reaction III. She was put on this medication of 1 mg. three times a day for six weeks, with all her symptoms but slightly improved.

*3, 4-bis (m-methyl-p-proprionoxy-phenyl) hexane is distributed under the name of "Meprane" by Reed and Carnrick, Jersey City 6, N. J.

TABLE I. SYMPTOMS

AUTONOMIC AND PERIPHERAL NERVOUS	NUMBER OF CASES	CURED	IMPROVED	UNAFFECTED
Hot flashes	43	41	2	0
Irritability	39	39	0	0
Sweating	40	40	0	0
Chills	40	40	0	0
Palpitation	20	18	2	0
Dyspnea	4	4	0	0
Vertigo	31	31	0	0
Headaches	4	2	2	0
Paresthesia	2	2	0	0
Pruritus	4	2	2	0
Arthralgia	2	0	0	2
Psychic				
Emotional instability	7	7	0	0
Melancholy	9	9	0	0
Weeping	21	20	1	0
Morbid worrying	17	15	2	0
Insomnia	20	18	2	0
Fatigue	20	18	2	0
Jealousy	1	1	0	0
Suicidal thoughts	1	1	0	0

The first patient was recently married for the second time. The second patient was cogitating a divorce from her husband who was given to heavy drinking. Such adverse family difficulties have been known to undermine therapeutic effects.

Patients were considered cured when all the symptoms disappeared at the end of the therapy. When one or two symptoms were unaffected they were considered markedly improved. When two or three symptoms were unaffected, as moderately improved. When most of the symptoms were unaffected they were considered as failures. The second courses were given only after an interval of two to three weeks when patients returned with recurrence of symptoms.

TABLE II. DURATION OF THERAPY

DEGREE OF IMPROVEMENT	NO. OF COURSES	2 WEEKS	3 WEEKS	4 WEEKS	6 WEEKS
Cured	52	4	25	22	1
Markedly improved	12	0	2	9	1
Moderately improved	5	0	0	5	0
Failure	2	0	0	0	2
Total	71	4	27	36	4

Dosages

The dosages were given on the trial and error basis in order to determine the proper therapeutic range. Seven of the patients were first given 1 mg. once a day for over a week, but this dose level was soon discarded because their symptoms were not at all improved. After a few trials we found the optimal dosages to be 1 mg. twice a day or 1 mg. three times a day. Also, from patients' own stories, we have discovered that we were securing the best results by giving the tablets 1 mg. three times a day or 1 mg. twice a day, rather than 3 mg. once or 2 mg. once a day.

Recurrence of symptoms took place very soon after discontinuing the therapy, i.e., seven to ten days. It seemed to be a better plan to put patients

on 1 mg. maintaining dose after the complete relief of symptoms. Most of these patients are now on this regime, and some of them have been symptom-free for over four months.

The 71 courses were given in the following manner:

Group I—1 mg. three times a day

21 first courses for 4 weeks
3 first courses for 3 weeks
4 second courses for 3 weeks
4 second courses for 2 weeks

Group II—1 mg. twice a day

15 first courses for 4 weeks
4 first courses for 6 weeks
20 second courses for 3 weeks

An outstanding feature of this synthetic estrogen was the fact that patients began to feel definite therapeutic effects within two to three days. Over 90 per cent of the patients volunteered the information that the number of hot flashes began to diminish about forty-eight to seventy-two hours after taking the tablets. Patients who took 2 mg. daily did fully as well as patients who took 3 mg. daily, with the exception, perhaps, that the full effect took place a few days later in the group taking 2 mg. per day.

We have obtained satisfactory cures in 64 courses out of 71, or 90.1 per cent, which is a very high index for an oral estrogen. Moderate improvement was obtained in five, and no relief in two. The background of the two patients who were refractory to this estrogen was mentioned above.

Vaginal Ph

When the estrogen titers are high there is an increased glycogen content of the superficial cell layers and vaginal secretions are acid. On the other hand, when low estrogenic titers are present, the glycogen content of the vaginal epithelial cells is minimum, and the Ph of the secretions is toward alkalinity. Estrogenic therapy restores the vaginal Ph to its normal state.

The Ph was studied by the use of nitrazine paper.

Ph 4.5—yellow
5.0—yellow brown } acid
6.0—yellow green
7.0—green—neutral
7.5—green blue—alkaline

On only 27 occasions vaginal Ph was beyond the range of 7.5. This turned acid gradually during the course of therapy. It was noted, however, that the Ph changes took place a few days ahead of the vaginal cytology.

Vaginal Smears

The vaginal cytology was classified according to Geist and Salmon.[2]

Reaction I.—Advanced estrogen deficiency. This is characterized by the complete absence of cornified cells and the preponderance of leucocytes and deep cells.

Reaction II.—Moderate degree of estrogen deficiency. The smear shows a variable number of irregularly shaped large epithelial cells, deep cells and leucocytes.

Reaction III.—Slight degree of estrogen deficiency. This smear is characterized by a predominance of irregularly shaped epithelial cells, occasional deep cells and leucocytes.

Reaction IV.—The smear shows mostly cornified epithelial cells. Leucocytes and deep cells are usually absent.

The vaginal smears of the 43 patients before the therapy were as follows:

Reaction I	Reaction II	Reaction III	Reaction IV
28	2	8	5

Only vaginal smears of reactions I and II were followed up carefully.

TABLE III. SMEAR CHANGES DURING THERAPY

	BEFORE THERAPY		TIME REQUIRED TO CHANGE FROM R I OR R II TO R IV			
	REACTION I	REACTION II	2 WEEKS	3 WEEKS	4 WEEKS	6 WEEKS
Group I 1 mg. three times a day	14	1	4	3	8	0
Group II 1 mg. twice a day	14	1	0	4	7	4

It is the writer's belief that vaginal smears taken from the clinic patients are not 100 per cent satisfactory. Vaginal douches, marital relations, and infection can all greatly alter the vaginal cytology. A human assay with a group of hospitalized patients is being carried on. We are hoping that in them, when all the above factors are eliminated and more frequent smears are being taken, we will be able to detect earlier vaginal responses.

Quantitative Urine Estrogens

Quantitative urine estrogens were studied before and after the therapy in six patients (Table IV). Each 24-hour specimen of urine was extracted according to the method of Kurzrok and Ratner.[3] The method of assays followed the rules of the standard technique set down by the League of Nations. Each assay was standardized against reference estrone.

TABLE IV. URINE ESTROGENS

PATIENTS	CONTROL	AFTER THERAPY
1 R. F.	184.0 I.U./24 hours	7,730 I.U./24 hours 1 week after the therapy of 1 mg. three times a day.
2 G. C.	417.0 I.U./24 hours	12,540 I.U./24 hours 2 weeks after the therapy of 1 mg. three times a day.
3 G. M.	833.0 I.U./24 hours	16,980 I.U./24 hours
4 R. R.	598.0 I.U./24 hours	12,560 I.U./24 hours 1 week after the therapy of 1 mg. twice a day.
5 E. O.	213.1 I.U./24 hours	14,010 I.U./24 hours 2 weeks after the therapy of 1 mg. twice a day.
6 A. P.	188.8 I.U./24 hours	15,030 I.U./24 hours 2 weeks after the therapy of 1 mg. twice a day.

TABLE V.

PATIENTS	CONTROL	AFTER THERAPY
1 R. F.	Negative	At least 2,000 I.U./Liter 1 week after the therapy of 1 mg. three times a day.
2 E. O.	At least 25 I.U./Liter	At least 750 I.U./Liter 2 weeks after the therapy of 1 mg. twice a day.
3 G. B.	Negative	Negative 1 week after the therapy of 1 mg. twice a day.
4 A. P.	At lease 25 I.U./Liter	At least 750 I.U./Liter 2 weeks after the therapy of 1 mg. twice a day.

Quantitative blood estrogen was estimated before and after the therapy according to the technique of Frank and Goldberger.[4] (Table V.)

The urine estrogen was greatly increased after the therapy from twenty to eighty times. The blood levels were likewise elevated in three of four cases tested. This indicated the high estrogenic titers in the body fluids, and showed that a large quantity of the hormone was being excreted through the urine.

Other Laboratory Studies

Basal metabolic rates were followed in ten patients. Only one obese patient had a basal metabolic rate of –19 per cent, and the rest were within the normal limits. There were no variations in basal metabolic rates during the therapy. The patient who had the basal metabolic rate of –19 per cent before the therapy had a rate of –17 per cent at the end of the course, six weeks later. Blood cholesterol, nonprotein nitrogen, and blood counts in the same ten patients revealed no changes during treatment.

The body weights of all the patients were checked at each visit. Most patients gained some weight after the relief of symptoms. The average gain for our 43 patients in 71 courses was 1.55 pounds.

Toxic Reactions

Patients were carefully questioned upon each visit as to any side reactions. Of the 43 patients treated during the 71 courses of therapy, only one patient reacted. Patient G. M. began taking 1 mg. three times a day. At the end of the third week she developed nausea, vomiting, headache, and fever. None of the other patients experienced the slightest discomfort in connection with this treatment.

Summary

1. 3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane is a highly efficient oral estrogen.

2. It relieves menopausal symptoms quickly and thoroughly.

3. Its therapeutic efficieney is 90.1 per cent, and its toxicity is 2.3 per cent.

4. It converted atrophic vaginal smears to the full estrogenic reaction.

5. It altered the vaginal secretions from alkalinity to acidity.

6. Careful quantitative blood and urine estrogen studies showed that it greatly elevated the estrogenic titers of the body fluids.

Conclusion

3, 4-bis (m-methyl-p-propionoxy-phenyl) hexane is a highly efficient oral estrogen with very low toxicity.

My thanks are due to Myra Glickman, B.S., for the technical assistance in this work.

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PSYCHIATRIC ASPECTS OF THE MENOPAUSE*

H. E. CHAMBERLAIN, M.D., SACRAMENTO, CALIF.

GYNECOLOGISTS, obstetricians, and psychiatrists, in reference to the study of womanhood, may, as diagnosticians, seem worlds apart and be made to appear in deep conspiracy, each against the other. As therapists, however, they can aspire to be as one, united in a common objective to aid women to develop their optimal femininity and to achieve motherliness with a minimum of destructive conflict.

Since it is the gross pathologies—the arrestments, deviations, and distortions—and our own professionally personalized interpretations thereof that tend to throw us apart, this presentation will therefore be limited to some aspects of one feature, i.e., the menopause, which we may all agree to as being physiologically initiated naturally, and thereby, we trust, we may discern in it the analysis of our common objective the better. And, although we will still have to contend with the influence of innumerable variables in three major sectors in the status of a given case, endowment, environment, and experience, nevertheless, for the purpose of clarity and unification, we may exclude that block of barren womanhood that reaches the menopause devoid of a history of conception or is childless. Even so, the frustrations and sublimations of reproductivity for women in our present culture so confuse the menopause state and obscure our conjoined efforts as such, broadly speaking, as to threaten our temporary alignment as therapists in general agreement, and with a common objective.

There is a general agreement that that phase of a woman's life when the capacity for reproduction is ending through the termination of menstrual function is the menopause. Furthermore, the descriptive literature in our respective fields is clear and concurred in, namely, that ovulation ceases through altered glandular activity; reproductive organs atrophy; and aging bodily changes traceable to both endocrinal and hormonal action occur. We all are familiar, too, and subscribe to the findings that studies in maturation, growth, and nutritional status, as determined in tissue metabolism, vitamin load, and excretion levels, serum proteins, ketosteroid and estrogen analyses, blood enzyme levels, and creatine/creatinine roles reveal. But the biochemistry and psychophysiology of fetal conduct, the psychosomatic stimulations and residuals of sexual congress, pregnancy, per se, delivery releases and postpartum supplements and nursing regimes—the appraisal of the significance of all these, to be more exact, and upon whom and when and where and for how long—tend to divide us and create dissension if not downright discord (with the

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pediatricians in the meanwhile running off with all, i.e., father, mother, and child, and in consultation conference and cooperation with each or all three). It is conceivable, too, that we might be in conflict therapeutically over the importance of men—one or many—in the history of any reproductivity that is terminated by a menopause. The absence of men or their presence or the uncertainty of too many or too few contacts, in phantasy or reality, cannot be ignored, so believe most psychiatrists, if a menopausal situation is to be observed accurately. Nor must pubertal impact, one's own or those of others in close proximity, be overlooked, so say the psychoanalysts.

Thus prefaced and with our common objective for womanhood—the preservation of optimal femininity and the protection of a constructive motherliness—substantiated, we can safely review the *psychiatric* aspects of the menopause, and in so doing imply some of the therapeutic procedures indicated and acquire the realization, too, that until further research has been accomplished that the exceptions to all our general assertions will be numerous enough in kind and sufficiently advanced in degree as to still create troublesome cleavages in our asserted unity.

The signs of the menopause which are common and whose presence contribute frequently to anxiety, fear, or guilt are easily enumerated for orientation purposes, i.e., vasomotor fluctuations ("flashes" or flushes, sweating, dizziness, "headaches," neuralgias, etc.); menstruation divergences (increases or decreases, interval changes, discharge changes, etc.); and psychic manifestations (excitability, depressions, insomnia, worry, etc.). In a day-to-day practice, gynecologists and obstetricians establish as good a rapport—as confidential—as psychiatrists do with disturbed womanhood. And these menopausal signs, their severity, and import are as evident to one as they are to the other. The initial distinction we each make arises, in my opinion, is not in the potential pathologies these signs may include or disguise or must be dealt with promptly at the outset, but in the fact that you have, as gynecologists and obstetricians, many more physical manipulations that you can turn to to bring relief, and therefore resort to more quickly. Whereas we are inclined to defer our evaluation to the determination of a life pattern—as related largely to the known factors which were heralded at puberty—and the sequence of events, imagined or in fact, established over the intervening years. This is laborious history taking that is also therapeutic and fraught with contradictions, identifications, and projections both false and factual, all equally motivating to symptoms and to intent. If a gynecologist or an obstetrician with a secure rapport with a patient endeavors to escape this task of evaluation, and even offers a partial release for the patient by a referral to a psychiatrist, many complications may be set in motion, i.e., the rapport is jeopardized, the patient can now infer, discard, or further decline and be additionally perplexed that the signs, in our professional minds, are truly more "mental" (emotional) than bodily (physical). Much more interpretation for referral than is ordinarily given must be practiced if we are to make the reciprocal gains by which we all would advance. By and large, much significant data go unmentioned in the best recorded histories in gynecologic

and obstetric clinics and practices, with the excuse that for the time being they are too time consuming to prepare or are irrelevant to actual treatment to be undertaken. This oversight or repudiation of information as currently handicapping or inconsequential may, at a later date, when the onset of the menopause obscures everything, be obtainable only by skillful detection from further distortion by dream or phantasy or compulsive inversions.

Many women not only seek to have allayed disturbing signs, but also must be assured fortification against the extension of retrogressive processes, i.e., beauty loss in particular. Compensatorially, the struggle to preserve this inherent femininity—beauty and biologic productivity, though cessation of the latter may be a welcome relief—assumes a drive or activity that should be recognized early and its dispensation arranged for. You have observed these manifestations many times over. They are so frantic in quality sometimes that you must yearn for a prompt resource referral, for those who abruptly seek another pregnancy to re-experience motherhood, or others who turn to pursuits or skills of a creative nature long dormant, especially since prepubertal days. In most cases we probably would agree as to the direction of therapy in the renewed drive for pregnancy, but the more sublimated creative drive we tend to argue about or dispose of as too superficial to squander our time over, though the degree of emancipation to be accomplished is deeply vested in the quality of the creative urge itself, i.e., intellectual, artistic, or moralistic. The entire field of family constellations is embroiled in this, namely, (1) the separation from one's children and not to feel shelved, (2) the acquisition of an in-law son or daughter and not to be free of jealousy; and (3) the renewal or extension of motherhood by substitution via grandchildren and not to be secretly scheming. It is vital to therapeutic procedure to help one in the menopause to anticipate a functioning role in family life, that does not usurp the lives of kin, or is not a torment to others, but instead aids one to muster her energies into productive pursuits and away from immobilizing debilitating conflicts . . . . There is a type of womanhood that in the menopause undergoes a heightened vitality that the layman dubs "dangerous and overdone." She denies her age and tries to belie it and often decries it in her contemporaries. Here in America, accessibility to an overabundant supply of cosmetic devices and purposefully designed fashions to help this self-delusion may be abetted, but actual therapy has to be more inclusive than this, in a postwar period, where men are returned to civilian life with an altered concept of womanhood generally, and much less passive toward the protection that such an older woman has frequently professed to offer.

In the menopause, as the instability or vacillation becomes dominant almost to the point of capriciousness, suggestibility becomes apparent, and exaggeration is common. It is true that these traits lessen inhibitions, arouse stimulating reveries, discolor sound judgment, and discredit symptoms (minimization or exaggeration). All life for some of these suddenly becomes most subjective or surcharged with personalization as their own atrophies and regressions accentuate their own depersonalization. Others, to bolster up an ebbing self-confidence, hurl themselves into a tightly devised isolation or solitary superiority.

In either of these situations the therapy to be considered must be basically protective and redirective—away from dangerous compromises, reckless "flings," exploiting companionships, disparaging rampages, or false retreats. Wherein paranoid features become conspicuous—toward devoted relatives or lifelong acquaintances—it is noticeable that suspicion and vindictiveness become marked, and most psychoanalytic schools would call our attention to sexual arrestments, deeply buried or well sublimated, either latent, overt, or perverted in whole or in part. The hostilities related hereto that are acted out are as likely to be directed toward the therapist as any other, and, accordingly, many of these patients find themselves being transferred eagerly from one therapist to another with here and there a questionable "quack" tossed in for extra measure all around and in sweet revenge!

Depressions, varying from transitory twinges to monopolizing states of melancholia, are common and may be accompanied by moods of ecstasy or elation or not. In some cases the grief and feeling of abandonment or desertion is all too true and justified—for they are engulfed by decline and set apart from others. Potentially suicidal as many are regarded to be, the essentials of therapy should stress in these cases, hygienic measures that strengthen, and a series of interviews which will desexualize the accumulated feelings of frustration, longing, and guilt. In these cases psychiatrists are prone to lay stress upon one's first experiences at the breast, the bowl, the bath, and the bed. The purposelessness and pallor of these depressive states in the menopause may be most misleading—"still waters run deep"—however mild on the surface and it doesn't suffice merely to activate the sluggish or to cap the filling cistern of conflicts. Together we must be more specific in our prescriptions—not simply to rely upon the arousal of interests in sports, artistry, social, or spiritual values, but actually decide on the additional factors gleaned from the individual's total life pattern which interests to deal with for how long and by and with whom and at what place and when, and then share the recorded results. And to curb the overactive cases by order or by drug may bring superficial quiet and simulated improvement, but in their wake the patient may be left to nurture hypochondriacal ideas, and clearly envision the impending doom, if not truly sense the gnawing of a beginning malignancy or to make it right sporting and really arresting confound one professionally with "a tumor that shows life." In these cases, although the immediate indications for palliative surgery may be expertly explained, the operation agreed to and flawlessly done, yet the cure, so called, does not occur and postoperative adhesions and stricture symptoms soon follow along and the diagnosis is belatedly now referred to as "a psychiatric or a functional condition" though it could have been both undetected or conventionally hidden lifelong and long before the menopause released the barriers to exposure.

One of the better texts, a definitive work in its own name, which delineates from a psychoanalytic point of view the complications inherent in any sex conduct, fancied or factual or inferred, that would profoundly affect the menopause has been written by Deutsch. It would be presumptive, indeed, to dis-

cuss the features of sexual adjustments before an informed group of gynecologists and obstetricians, and to furnish you with any information not already well known to you. There is, however, one feature of the menopause, referred to earlier, and explained at length in the book by Dr. Deutsch to which your attention should be called to especially. It is the feature of depersonalization. As the loss of femininity increases and the reproductive capacity diminishes, there comes to the forefront more noticeably in a woman's life in the menopause elements of masculinity. To whatever degree it was masked throughout life or distorted or sublimated or repressed, the physical changes in the menopause help to make these elements more real and the component emotional elements more apparent. It may or may not concern the patient herself. You too may know what to do about it per se, or seek to minimize it or simply condone it as inevitable or "one of those inescapable things we just have to put up with." If shocked in the extreme by it, many women cannot discuss these manifestations openly or freely, and if she is a new patient to you it is exceedingly hazardous to have it brought out by a therapist. Not infrequently it is of grave concern to others, especially to children, and more specifically to husbands, sons, uncles, brothers, or fathers. Many adult men find it excruciating, so to speak, to confer with a gynecologist or an obstetrician when their womenfolk are in the twilight zone of reproductivity and beginning to adopt a masculinity of their own. Many women, too, are reluctant while in the menopause, except for retaliative purposes perhaps, to defend adequately her request uncompromisingly that the male in her life be consulted regarding her own threats of and to masculinity. Personally, I suspect that were we to share the notes of our consultations we would find the preponderance of confirmation that these males are in our psychiatric files—hard as it was for them too to see a psychiatrist—as patients themselves or regarding how best the woman in their lives can be treated or should be handled, whereas she continues blithely to be content to receive gynecologic care, though emancipated well and good from obstetrics. Surely our best united efforts could first be concentrated on these situations—monopolizing to all of us—and perhaps a segment of marital discord could be alleviated and many in middle-age look forward to a happier and a more harmonious old age together than is now anticipated by them. And a further implication beyond the need for a perfected united service between us in these divided situations is that all—gynecologist, internist, obstetrician, neuropsychiatrist, or surgeon—who treat those in the menopause should also be conversant with involutional states and the field of geriatrics. It is a questionable practice that simply takes a woman through the menopause nobly and then leaves her confronted, head-on, with an old age, uninspired and hopeless!

Treatment for the menopause, as outlined by gynecologists or obstetricians, and that which psychiatrists would propose in simplified form is for the most part similar in type, i.e., hygienic, supportive and protective, regulative, and directive. We vary most in the application of disciplinary measures and the evaluation of conflicts as expressed by the patient. Throughout this presentation it is obvious that in the selection of significant factors in our history taking,

we could be at wide variance and even be in conflict ourselves over the relative merits of any one factor and its subsequent appraisal. However, confidence in one another and a cooperative effort to interrelate and to correlate our differences on each case individually would go far to assure to women in the menopause a degree of increased comfort not now available to but a very few.

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CESAREAN SECTION MORTALITY IN THE HOSPITALS OF A SMALL COMMUNITY—A DEFENSE OF THE PROCEDURE*

R. ALFRED GANDY, M.D., STAMFORD, CONN.

(From the Department of Obstetrics and Gynecology, Stamford and St. Joseph's Hospitals)

THE primary purpose of this study is to investigate the frequency of cesarean section in the city of Stamford and to determine whether or not we are practicing good obstetrics, relative to this operation.

Stamford has a population, including several small peripheral communities, of about seventy thousand. There are two hospitals in Stamford. Since the obstetric department in each hospital is approximately the same size, there being a total of 70 obstetric beds, and since the same physicians practice in both hospitals, the figures represent the combined results from the two institutions. Both hospitals are "Open Staff" hospitals with a total of 35 doctors practicing obstetrics in the institutions. The cesarean sections were performed by eight operators. Three of the eight operators do nothing but gynecology and obstetrics, while the other five do general work.

The study covers a period of nearly six and one-half years, from October, 1939, to July, 1946.

During the period of this study just under 99 per cent of the deliveries in the city occurred in the hospitals. Over 90 per cent of the patients were private cases. The private patients received their prenatal care from their own doctor, while the staff cases received similar care from the clinic or had no prenatal care.

Because of the type of obstetrics in Stamford, practically all private cases and practically all delivered in the two hospitals, we should anticipate better results than in those institutions which serve a high proportion of staff cases or are located in a community where there are many normal home deliveries which never reach the hospital records.

Since October 1, 1939, we have had 8,107 hospital deliveries with 13 maternal deaths, a rate of 0.16 per cent, or 16 per 10,000 deliveries. We have performed 531 cesarean sections, an incidence of 6.5 per cent. Four cesarean deaths have occurred, a cesarean mortality rate of 0.75 per cent. Of the four cesarean deaths, one was an elective cesarean, making our elective cesarean mortality rate 0.18 per cent. All figures are uncorrected.

A careful study of recent statistics indicates that we do more cesarean operations in Stamford than are performed in most communities and in most teaching hospitals. I have endeavored to the best of my ability to determine whether or not we are justified in continuing our high cesarean rate based on our own results.

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TABLE I.

YEARS	NUMBER OF CASES	AUTHOR, HOSPITAL	INCIDENCE OF CESAREAN		CESAREAN MORTALITY UNCORRECTED	CESAREAN MORTALITY FACTOR
1935–1945	10,818	Thoms, New Haven	average	5.9%	.31%	1.8
			ward	3.2%		
			private	9.6%		
1932–1943	68,786	Waters, Jersey City		2.67%	1.0%	2.7
1931–1944	39,709	Dieckmann, Chicago		4.74%	.61%	2.9
1932–1939	27,125	N. Y. Lying-in		2.1%	1.7%	3.6
1939–1946	8,107	Gandy, Stamford		6.5%	.75%	4.9
1934–1943	1,887 Cesareans	Irving, Boston	average	4.2%	1.3%	5.5
			ward	3.2%	1.4%	
			private	6.7%	1.1%	
1938–1942	4,875	Nash, Kansas City		7.1%	1.1%	7.8
1932–1941	750 Cesareans	Eastman, Baltimore		5.5%	1.8%	9.9
1931–1941	23,396	Barney, Cleveland	average	6.1%	1.7%	10.4
			ward	6.3%	3.3%	
			private	6.0%	.5%	
1932–1942	22,754	Mohler, Philadelphia	average	5.8%	1.96%	11.4
			ward	3.6%	3.17%	
			private	9.58%	1.15%	

In order to more easily evaluate the statistics contained in the above table and similar tables, I am introducing a new term which I will call the "cesarean mortality factor." In most tables relative to cesarean section there are two variables, the incidence of the operation and the mortality from the operation. The cesarean mortality factor is a combination of these two factors in their proper relation on a basis of ten thousand deliveries. The factor is the actual number of deaths in the institution which may be expected among the cesarean patients for each ten thousand deliveries. For example, if the cesarean factor is five there are five cesarean deaths for each ten thousand women delivering babies. When the cesarean mortality factor is low there are few deaths chargeable to the operation, regardless of the number of operations performed; when the factor is high, there are many deaths chargeable to the operation, regardless of the percentage of operations performed. I feel this gives a much clearer picture of the lives lost as a result of the operation than do simple percentages of operations performed and the mortality percentage for those operations. One would expect that as the number of operations increased the cesarean mortality factor would increase. In general this is true, but the exceptions are outstanding. The institution with the lowest cesarean mortality factor performs operations on 5.9 per cent of all admissions; the institution with the highest factor performs the operation on a similar percentage of 5.8. It should be our aim to keep the cesarean mortality factor as low as possible, regardless of the percentage of operations performed in achieving this end. In Stamford, though we have performed cesareans on 6.5 per cent of our pa-

tients, the cesarean mortality factor compares favorably with that of the other institutions mentioned in the table.

The above statistics have been chosen because each is from a well-known institution in a different part of the country, and all figures are relatively recent, none antedating 1931. Earlier figures are at such variance with more recent statistics that I do not feel they are helpful in determining present-day policies.

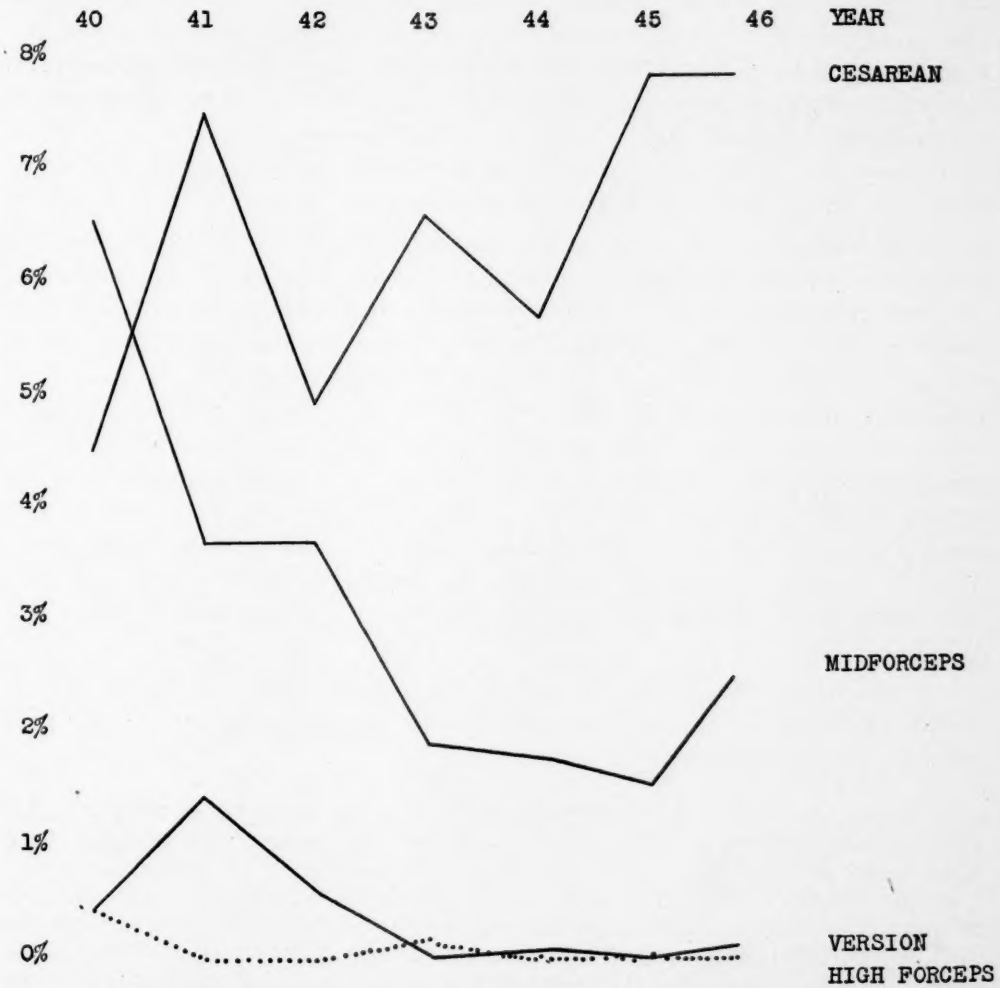

Fig. 1.—Percentage of annual cesareans, midforceps, versions, and high forceps, October, 1939, to July, 1946.

Even the cesarean mortality factor is only a partial answer to the over-all mortality picture. By doing more cesareans, especially the elective operation, one would expect a lessening of complicated vaginal deliveries. In our hospitals we have many more maternal deaths occurring from noncesarean patients than from the cesarean group. If the complicated vaginal deliveries can be lessened materally by doing more elective cesareans, I feel that our ultimate ma-

ternal mortality will be improved. That the above is actually occurring in Stamford is shown in the above illustration. As examples of complicated vaginal deliveries I have chosen versions, high forceps, and midforceps. Since 1940 our cesarean rate has gradually increased from 4.3 per cent up to its present level of 7.8 per cent. With this increase, and most of the increase is in the elective cesarean group, versions have dropped from a high in 1941 of 1.4 per cent (twelve) to practically 0, there having been only two versions in the last three and one-half years. The high forceps rate in 1940 was 0.45 per cent (four); in 1943 the rate was 0.13 per cent (two), and there has not been a high forceps delivery since 1943, two and one-half years. The midforceps operation which carries about the same hazard to the mother as a cesarean, according to Irving, has dropped from a high in 1940 of 6..6 per cent to a low in 1945 of 1.6 per cent. I believe that the lessening of the complicated vaginal deliveries is at least in part due to the increase in elective cesareans.

Keeping in mind the above changes in our methods of caring for obstetric patients in Stamford during the last six and one-half years, let us inquire into our final maternal mortality. Our uncorrected maternal mortality in Stamford has been 0.16 per cent, or sixteen deaths per ten thousand deliveries, during this period. For the State of Connecticut as a whole between 1939 and 1943 the maternal mortality was 0.22 per cent, or twenty-two per ten thousand births. For the United States in 1942 the maternal mortality stood at 25 per ten thousand births. Chicago in 1944 reported a maternal mortality for the city of 16 per ten thousand births. Chicago Lying-in Hospital reported 17 per ten thousand births between 1931 and 1945. Waters from Margaret Hague Hospital reports a mortality of 29 per ten thousand between 1932 and 1943. The New York Lying-in Hospital reports 24 per ten thousand between 1932 and 1939.

I would now like to discuss each of our thirteen maternal deaths and ascertain their relation to the high incidence of cesarean sections. First, let us consider each of the four cesarean deaths.

CASE 1.—(3610) A 33-year-old white woman, para vi, gravida vii, had recently spent eleven months in a tuberculosis sanitarium. She became pregnant while she was still there. At the seventh month of pregnancy she had a profuse vaginal hemorrhage and was admitted within an hour. A diagnosis of tuberculosis and placenta previa was made. Because the hemorrhage was still uncontrolled at the end of two hours, and labor had not started, a cesarean operation was performed. We recovered a premature stillborn child; the vaginal hemorrhage promptly stopped and did not recur. The patient received plasma immediately after the operation, blood one and one-half hours postoperatively, then glucose. The plasma and glucose were repeated that same operative day. The following day she received more blood and glucose. At this point the hemoglobin was 32 per cent. Her course was progressively downhill and she died on her fifth postoperative day. There was no postoperative hemorrhage; her abdomen remained soft and there was very little fever until just before death. The patient repeatedly coughed up blood. It was felt the cause of death was irreversible shock from the blood loss, to which no doubt the operation contributed. I feel the chief criticism of the way this

patient was handled was the delay in getting in adequate amounts of blood promptly. Her first transfusion was given one and one-half hours postoperatively, her second the next day, and her third on the fourth postoperative day. We had no blood bank at this time and it was difficult to get adequate amounts of proper blood promptly. We now have a blood bank. I feel we can say the cesarean contributed to this patient's death, but I do not feel it proper to say the cesarean caused this death.

CASE 2.—(105372) A 29-year-old woman with her first delivery had a fifty-hour trial labor, an attempted version, and an attempted forceps delivery. Finally a cesarean section was performed, followed by death on her fourth postoperative day from pelvic peritonitis. The criticism here is obvious: too long a trial of labor, a cesarean after contraindications had risen to a high point, failure to follow the cesarean with a hysterectomy. With this case I cannot blame the operation for the death, but rather the delay in doing the operation. A little less conservatism in the early part of this labor might well have given us one less maternal mortality.

CASE 3.—(114237) A 48-year-old white woman who had had a previous cesarean operation had an uneventful convalescence till her eighth postoperative day, when she had a pulmonary embolus and died within a few minutes. This represents our only elective cesarean death. The operation must be held responsible.

CASE 4.—(124819) A 25-year-old white woman with a slightly contracted pelvis was given a sixteen-hour trial labor. Her uterus was found to be in tonic contraction, and she died on her seventh postoperative day from paralytic ileus. This we must accept as a cesarean death after a reasonable trial of labor.

In reviewing these four cesarean deaths can we hold the frequency of our operations accountable? The patient in Case 1 did not receive adequate quantities of blood soon enough. With or without a cesarean, under these circumstances, probably the result would have been the same. In case 2, had the operation been performed more promptly rather than not at all, I feel the outcome would have been better. In Case 3, I feel the patient should have had a cesarean, and no other form of treatment would have increased her prospects for survival. The patient in Case 4 with a slightly contracted pelvis was given an adequate trial labor followed by section.

Now let us take up the noncesarean deaths.

CASE 5.—(123578) The patient was delivered at home three days before admission. She was admitted to the hospital on the medical service because of heart failure, and died from heart failure two days after admission.

CASE 6.—(120021) After a four and one-half hour labor, the patient was delivered by low forceps. No laceration resulted. The patient died on the twenty-eighth postpartum day from lobar pneumonia.

CASE 7.—(108589) The patient had a six and one-half hour labor and was delivered by low forceps. Shortly after this easy delivery, the patient went into shock. After a delay of some hours, the patient was found to have an inverted uterus which was replaced with difficulty. The patient died later the same day.

CASE 8.—(103355) An incomplete infected abortion had occurred between three and four months. The patient died from septicemia and peritonitis after eighteen days in the hospital.

CASE 9.—(3499) The patient, aged 25 years, had a rheumatic history. This was her second delivery. The patient had a brief labor. She coughed excessively and died on her first postpartum day from "Exhaustion due to cardiac asthma and acute pulmonary edema."

CASE 10.—(495) The patient was 39 years of age, with rheumatic heart disease. The last three months of pregnancy were spent in bed because of heart failure and decompensation. She was delivered in bed because of cardiac condition. This was her tenth child, delivered spontaneously after a three-hour labor. She died on her third postpartum day from heart failure.

CASE 11.—(2139) A primipara, aged 38 years of seven months' gestation. She had several hemorrhages at home and was admitted in labor and bleeding. Diagnosis of premature separation was made. Following an eight-hour labor a version was done and the child was delivered. There was a postpartum hemorrhage and the patient died two hours after delivery. Here is a case where I believe a cesarean does enter the picture. A 38-year-old primipara with a premature separation in the opinion of some is handled in a safer fashion by prompt cesarean section than by an eight-hour labor and version.

CASE 12.—(93663) This patient, aged 28 years, was delivering her second child. Following a sixteen-hour trial labor, an attempt to deliver the child with high forceps failed. A version and extraction was performed with difficulty and the mother died one hour later. In this case I feel cesarean enters the picture. If so little progress has occurred after sixteen hours of labor that the head has barely engaged, and there is some reason for delivering the patient, cesarean is a safer procedure than either high forceps or version, or both.

CASE 13.—(104100) A primipara, aged 34 years, after thirty hours of trial labor the head was found to be in the midpelvis and not progressing. Delivery was attempted with midforceps and failed. A version and extraction was done with difficulty and a stillborn child obtained. The mother died about six hours later. Had we regarded this patient as an elderly primipara and done en elective cesarean I feel her prospects would have been better. Failing this, had we recognized that labor was progressing unusually slowly, and performed a cesarean after a short trial labor before vaginal instrumentation, her prospects would have been better.

Conclusions

1. A new term has been introduced, "cesarean mortality factor," which facilitates comparing and comprehending cesarean mortalities. The factor is the actual number of cesarean deaths to be expected for each ten thousand deliveries.

2. The cesarean rate in Stamford during the last six and one-half years has been 6.5 per cent, and is still rising.

3. Our cesarean mortality factor compares favorably with other institutions.

4. As our cesarean rate has constantly increased, our complicated vaginal deliveries have constantly decreased.

5. A careful study of our cesarean deaths does not indicate that another method of delivery would have saved many of these cases.

6. A careful study of our noncesarean deaths does indicate that some lives might have been saved by a more liberal interpretation of csearean indications.

7. Our ultimate maternal mortality of 16 per ten thousand births during the period of this study is commendable. I feel that our use of cesarean sections has contributed to this figure.

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65 South Street

MANAGEMENT OF POSTABORTAL PERITONITIS*

HENRY C. FALK, M.D., F.A.C.S., AND GEO. BLINICK, M.D., NEW YORK, N. Y.
(From the Gynecological Service, Harlem Hospital)

AN ANALYSIS of the pathogenesis and associated pathologic findings in 61 fatal cases of postabortal peritonitis proved that the most common pathway of infection from the endometrium to the peritoneum was by direct extension through the tubes.[1] Infection of the peritoneum by way of the parametrium and myometrium was less frequent.

The medical treatment of postabortal peritonitis, exclusive of perforation, was wholly unsuccessful. Not one patient who was proved to have postabortal generalized peritonitis recovered. Baisch,[2] Latzko,[3] Jesierski,[4] and others have had similar experiences. Since 1941, the entire problem has been restudied, and selected cases of postabortal peritonitis have been treated with surgery.

Surgery must be preceded by accurate diagnosis. As a result of clinical experience correlated with postmortem studies, it has been found that abortion may be classified into six main groups.[5]

Type I.—Endometritis; the infection is limited to the cavity of the uterus and there is no evidence of extrauterine extension.

Type II.—Parametritis; cellulitis of the broad ligament. The infection has extended to the extraperitoneal supporting tissue of the uterus.

Type III.—Thrombophlebitis; the infection has extended to the uterine or ovarian veins. The thrombus may be fixed to the vein, or showers of infected emboli may be cast off.

Type IV.—General sepsis in which bacteria lights on the heart valves and are disseminated from this site.

Type V.—Generalized peritonitis.

Type VI.—Perforation of the uterus.

The usual signs and symptoms of generalized peritonitis are well known and need not be described. There are, however, some features of generalized peritonitis peculiar to postabortal disease which require clarification.

In patients who are seen at Harlem Hospital, the peritonitis is usually fulminating in nature, and death occurs rapidly. The majority of these patients have had induced abortions, many with the crudest instruments and lack of asepsis. In such cases the diagnosis is self-evident, and the problem is whether the patient, despite intensive supportive therapy, is able to withstand the further shock of surgery.

In a smaller, but not inconsiderable number of patients, a milder course may prevail, as in patients who lived from fourteen to forty-eight days after hospitalization. Localization of pus between the intestines, in the lumbar gutter, the pelvis, and subphrenic regions is common. On abdominal and vaginal

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examinations, these localized intraperitoneal abscesses may have been interpreted as parametric exudates until death; autopsy then shows a generalized peritonitis. However, since these masses are formed as a conglomeration of abscess, induration, distended bowel, and adherent omentum, their outline characteristically undergoes frequent change; *a pelvic or abdominal mass which undergoes daily variation in outline is considered to be pathognomic of this type of peritonitis.* In many such cases, it may seem as though the patient will finally recover. The abdomen may become soft, the mass disappears either spontaneously or through drainage, a hopeful prognosis is considered, and then the patient dies from chronic sepsis as determined by autopsy.

General peritonitis caused by a perforation of a parametric or tuboovarian abscess directly into the peritoneum is castrophic, and fortunately rare. It may be recognized by the sudden appearance of shock, high fever, and signs of peritonitis in a previously comfortable patient with postabortal parametritis.

The diagnosis of associated thrombophlebitis is rarely made clinically. It has been found difficult to palpate thrombosed veins with any degree of certainty. The overwhelming clinical picture of peritonitis masks any local signs and, in the rare case in which metastatic emboli are found, the signs of pulmonary infection are often indistinguishable from the signs of terminal bronchopneumonia.

In the differential diagnosis, a history, or clinical evidence of recent pregnancy or abortion is essential for an accurate differentiation from other forms of peritonitis such as those caused by a perforated appendix, ruptured pyosalpinx, perforated peptic ulcer, etc. As a result of fear or ignorance, an incorrect history is often obtained. If vaginal bleeding is present, every effort to obtain an accurate history should be made, and the possibility of a postabortal infection as a cause of peritonitis must always be considered.

From a gynecologic point of view, the most important syndrome to be differentiated from postabortal peritonitis is parametritis with evidence of peritoneal irritation. Not unfrequently a patient with parametritis has peritoneal irritation as evidenced by tenderness, rigidity, and distention of the abdomen. The peritoneum covering the broad ligament appears lusterless, shaggy, and edematous. There is little increase in peritoneal fluid.

In such patients the signs of peritoneal irritation subside within twenty-four to forty-eight hours of expectant treatment. In early cases of parametritis, examination of the rectovaginal septum has proved to be of some aid. In these cases, a tonguelike thickening is frequently observed, whereas this is rare in the early stages of spreading peritonitis.

Although many gynecologists consider patients with parametritis and associated peritoneal edema as having peritonitis, involvement of the general peritoneal cavity does not exist. This is the type of case to which the term "peritonismus" could be applied. While a local pelvic peritonitis may be present, there is no evidence of spreading peritonitis, and the two must be clearly differentiated. The inclusion of such patients with those of generalized

peritonitis causes the mortality and morbidity rate to be lowered; thus a false impression is created with respect to the prognosis and efficacy of treatment.

The differential diagnosis of peritonitis secondary to perforation of the uterus is impossible except by accurate history or evident signs of perforation such as bowel or omentum projecting into the vagina or x-ray visualization of foreign bodies such as catheters in the abdominal cavity. If, as will be shown, early surgery is adopted as the guiding principle for all postabortal peritonitis, such differentiation is unnecessary.

Finally it should be clearly understood that the patients who are observed at Harlem Hospital are usually admitted in the late stage of peritonitis. Except for a sporadic case, the peritonitis is present on admission.

The duration of peritonitis preceding hospital admission is, of course, conjectural; however, the average history of bleeding in patients with postabortal peritonitis is ten days before admission to the hospital. The importance of this from a surgical viewpoint is that early surgery is rarely possible, a fact which will be more fully discussed later.

Therapy

It has been aptly said that the cure of puerperal fever is of secondary importance compared to its prevention. The sulfonamides and penicillin present a very great advance in the prevention and treatment of postabortal infection. It is well known that para-amino benzoic acid found in pus and necrotic tissue inhibits the chemotherapeutic action of the sulfonamides, thereby rendering them ineffective in the treatment of postabortal peritonitis. On the other hand, penicillin might seem *a priori* to furnish a cure. However, this has not proved to be so, since, notwithstanding these advances, from five to eight cases of generalized peritonitis, are still seen each year at Harlem Hospital. This incidence is identical with that prior to the chemotherapeutic era. Other forms of postabortal infection such as parametritis and blood stream sepsis have markedly diminished, but peritonitis is still seen in identical proportions. Why this should be so is not clear, but there is no doubt from our own statistics that this is a valid statement.

Hysterectomy for puerperal fever is thought to have been first performed by B. S. Schultz in 1886. Since that time there have been numerous reports of surgery for postabortal and puerperal peritonitis, particularly in the European literature. Unfortunately in many reports the etiology and extent of the peritonitis, as well as the exact details of operative management, are not made clear. In general, the German gynecologists have preferred incision and drainage of the peritoneum with or without the instillation of antiseptics into the abdominal cavity. Thus Latzko was able to obtain 24.2 per cent cures in 335 cases following abdominal incision and drainage. The best results were obtained when intervention was done within the first forty-eight hours of illness. Halban and Koehler[6] stated that the recovery rate is 32 per cent if operation is performed within twelve hours. Thereafter the percentage diminished so that after seventy-two hours surgery is useless and death was inevitable in diffuse peritonitis. Koblanck[7] reported 44 cases, of whom 20 per cent recovered. Jerserieski reported 75 cases of postabortal peritonitis; 28 were not operated upon, and all died. The remaining 47 were operated upon and 25 per cent recovered. Döderlein preferred vaginal drainage. Simon, of his clinic, reported 37 recoveries in 50 cases of colpotomy. This report includes,

however, "circumscribed pelvic peritonitis." Farrari, Houel, and Johier[9] report four recoveries in five cases in which they performed a subtotal hysterectomy with ligation of the veins.

In the United States, surgery has not been widely used in postabortal peritonitis. Baldwin,[10] however, has strongly advocated hysterectomy with or without ligation of the veins, a procedure which has largely been neglected. A total of 80 patients was operated upon, with a 25.5 per cent mortality. Of his last six patients all recovered. Polak[11] reported 15 cases—seven were incised and drained, with five deaths; eight were managed conservatively, with six deaths. He states "we have learned by bitter experience that puerperal and postabortal infective processes are actually extended by manual and instrumental manipulation."

In our own experience, medical treatment including sulfonamides and penicillin in varying dosages and routes of administrations, fluid balance, the use of small and large repeated transfusions, serums, vaccines, various nonspecific therapies, oxytocics, Wangensteen drainage, etc., have been of no avail and do not merit extended discussion. The first known case of recovery from postabortal peritonitis at Harlem Hospital was encountered in 1940. A patient mistakenly considered to be suffering from ectopic pregnancy was found to have an early spreading peritonitis. The uterus was somewhat enlarged, boggy, and the tubes inflamed. Uncertain of the exact pathology, a supracervical hysterectomy and bilateral salpingectomy was performed. On pathologic examination the uterus was found to contain infected placental tissue and the tubes to be the seat of a severe suppurative endosalpingitis. This patient made an uneventful recovery. Eight other cases of postabortal peritonitis observed in that year died under conservative management. It was then decided that henceforth surgery should be tentatively utilized, since the prognosis of suppurative peritonitis after abortion was inevitably fatal without operation.

In 1941 and 1942, 12 peritonitis cases were seen. In three, abdominal incision and drainage with the use of intraperitoneal ether and extensive drainage was employed; all three died, as did the nine nonoperative cases. In all, large amounts of sulfonamides were used. It was concluded that in the patients seen at Harlem Hospital the disease was of too long duration on admission for drainage alone to be effective.

It was then decided that hysterectomy should be done. Since that time, in the years of 1943, 1944, 1945, and the early months of 1946, 24 cases of peritonitis have been observed. Thirteen were not operated upon, but were given the most expert and attentive palliative therapy possible, which included frequent transfusions as well as large doses of sulfadiazine and, in 1945, large doses of penicillin as well. All 13 patients died. The remaining 11 patients had a total or subtotal hysterectomy performed; seven of these recovered, a recovery rate of 63 per cent.

The details of the 11 operative cases since 1943 are summarized in Table I. In 1943, two total abdominal hysterectomies were performed in which the pelvis was widely drained through the vault of the vagina. Both patients died. It was felt that the operating time could be shortened and the same results accomplished by supracervical hysterectomy, with splitting of the posterior lip of the cervix so as to permit wide drainage of the pelvis through the opened cervix by means of multiple Penrose drains. This routine has since been adopted.

The abdomen is opened through a left paramedian incision with the patient in moderate Trendelenburg position. A self-retaining retractor is inserted and the pus lying free in the peritoneal cavity is suctioned or soaked up with

TABLE I

	NON-OPERATIVE	RESULTS	NUMBER OF OPERATIONS	TYPE OF OPERATION	RESULTS
1940	7	All died	1	Supracervical hysterectomy	Recovered
1941	5	All died	2	Incision and drainage	2 Deaths
1942	4	All died	1	Incision and drainage	1 Death
1943	3	All died	2	Total hysterectomy	2 Deaths
			1	Supracervical hysterectomy	Recovered
1944	6	All died	2	Supracervical hysterectomy	2 Recovered
1945	4	All died	2	Supracervical hysterectomy	1 Died
					1 Recovered
			1	Total hysterectomy	Recovered
1946	0	0	3	Supracervical hysterectomy	2 Recovered
					1 Died

pads. No attempt is made to break up any intestinal adhesions except those to the pelvic organs, and these are rarely an important or prominent feature. The intestines are walled off with three laparotomy pads, and the uterus, tubes, and ovaries clearly exposed. A routine supracervical hysterectomy and bilateral salpingo-oöphorectomy is then performed. The tissues are markedly friable and suture-ligatures are usually preferable to clamps. After the uterus, tubes, and ovaries have been extirpated, the posterior cervix is grasped with two tenaculi and with a straight Mayo scissors, the entire thickness of the posterior cervix is incised down to the vagina. Caution to see that the rectum is not injured is obvious. As a result of this incision, the whole cervix is widely patulous. Hemostasis of the cervix is secured by a running lock stitch applied to the two cut edges of the cervix, extending from the internal os to the vagina.

From five to seven Penrose drains are then inserted through the bisected cervix to the peritoneum. Ten grams of sulfanilamide are dusted over the pelvic peritoneum and the sigmoid colon is carefully placed across the pelvis to exclude the general peritoneal cavity and minimize the possibilities of postoperative intestinal adhesion with obstruction. The abdomen is closed tightly in layers. The skin is drained with a small Penrose drain in the lower angle.

The reason for the choice of patients submitted to surgery is difficult to evaluate. Some patients were moribund upon admission. In two patients severe jaundice present on admission caused pardonable reluctance to institute surgery. These variable factors resulted in the division of cases into two groups; the first of 13 nonoperated cases with 100 per cent mortality and the second of 11 operated cases with 63 per cent recovery. Except for surgery, all received identical therapy so that the advent of chemotherapy in recent years cannot solely be responsible for the improvement in the reported results, although undoubtedly penicillin was of inestimable benefit in aiding recovery. Penicillin alone, even in fairly large doses, did not cure a single case. Recently Douglas[12] has reported a single case with recovery following large doses of penicillin and multiple incision and drainage of localized intra-abdominal abscess. It is our intention to employ much larger doses of penicillin and streptomycin than has hitherto been available. The last patient who was operated upon appeared to be moribund preoperatively. She was given 1,000,000 units of penicillin intravenously immediately on admission while awaiting preparation of the operating room and showed a dramatic clinical improvement. At the present time it cannot be said whether such heroic doses would be successful without the use of surgery.

In no case has vein ligation been done. From autopsy experience, it does not seem as though the type of thrombophlebitis which may accompany peritonitis is in itself responsible for generalized sepsis or major embolic phenomena. This is reflected clinically in the fact that repeated blood cultures in cases of peritonitis were positive in less than 3 per cent of all cases studied. Furthermore, sepsis from thrombophlebitis was not the cause of death in any of the patients who died.

In the discussion of Baldwin's work, two objections were repeatedly expressed. The first was the uncertainty of preoperative diagnosis, and the second the difficulty of the operative technique required. As to diagnosis, there can be little doubt that Baldwin did operate on many patients with parametritis and so-called thrombophlebitis as well as generalized peritonitis. There also can be little question that it is rare to see death ensue from parametritis. Careful medical therapy including cul-de-sac drainage when abscess ensues is invariably successful. Thrombophlebitis responds well to supportive and chemotherapy, and to date we have not had recourse to surgery in such cases. As a result of cumulative experience with a large abortion service in a municipal hospital, the diagnosis of these types of postabortal infection does not usually present great difficulties, and we believe that by careful analysis of each case, generalized peritonitis can be readily diagnosed preoperatively according to the criteria previously discussed.

Careful clinical observation permits an accurate diagnosis almost without exception. It is to be expected that a rare error in diagnosis will occur, but such an error seems negligible in relationship to the fatal course of the nonoperative cases. The risk of laparotomy in such mistaken cases would not seem to be greater than that undertaken for a mistaken diagnosis of acute appendicitis. To date, such an error has been made on only one occasion. The abdomen was closed without further surgery, and her convalescence was uneventful.

Abdominal or cul-de-sac puncture for diagnosis has been considered, but the risk of false information and the dangers of its performance when distention is present has discouraged its use. It is stressed that the diagnosis of generalized peritonitis can be made with considerable certainty clinically, that such cases are invariably fatal and hysterectomy is reserved only for such cases in which this fatal outcome has been shown to be inevitable by experience.

Patients with spreading postabortal peritonitis as described herein are generally seen only on the service of large municipal hospitals and rarely if ever in private practice. Preventive measures in such patients are not possible since almost all are admitted after the onset of spreading peritonitis. Medical treatment including chemotherapy with the sulfonamides and penicillin alone have not resulted in any known cure to date. On the other hand, supracervical hysterectomy and bilateral salpingo-oöphorectomy with splitting of the cervix and drainage combined with penicillin has dramatically cured two-thirds of patients operated upon.

Summary

1. The management of spreading postabortal peritonitis exclusive of perforation of the uterus is discussed. If patients with localized pelvic peritonitis secondary to parametritis are not included in this group, all known patients with generalized peritonitis following abortion have died regardless of the type of medical therapy employed including the use of both sulfadiazine and penicillin.

2. Of three cases of postabortal peritonitis observed in 1941 and 1942, treated by incision and drainage of the peritoneal cavity in addition to intensive sulfathiazole therapy, all died. It is believed that the cases seen at Harlem Hospital are too far advanced for simple incision and drainage to be effective.

3. Since 1943, 24 cases of generalized postabortal peritonitis have been seen at Harlem Hospital. Thirteen were not operated upon and all died. Of 11 patients following hysterectomy, with splitting of the cervix and vaginal drainage, eight have survived.

4. From these findings, hysterectomy and bilateral salpingo-oöphorectomy with splitting of the cervix and vaginal drainage in conjunction with appropriate chemotherapy, multiple blood transfusions, and intestinal drainage (Levin Tube, Wangensteen apparatus) is urged as the most effective therapy yet devised. For technical reasons, and to decrease shock, supracervical hysterectomy with splitting of the posterior lip of the cervix and the insertion of multiple drains into the pelvis is preferred to total hysterectomy. Vein ligation was not employed, and is not deemed an essential adjunct to surgery.

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INDICATIONS FOR REMOVAL OF A NORMAL UTERUS

ROLAND E. BIEREN, M.D., AND J. MASON HUNDLEY, JR., M.D., BALTIMORE, MD.
(From the Department of Gynecology, University of Maryland, School of Medicine)

IN THE ten-year period prior to August 1, 1946, there were 1,701 hysterectomy specimens received by the pathologic department of this institution. Of these, 300 were reported as normal. This report is the result of a critical review of these 300 cases, and represents an effort on our part to arrive at definite conclusions concerning removal of a normal uterus.

Comment

1. Conditions which may be considered definite indication for removal of a normal uterus are:

Malignancy.—The fourteen cases with pelvic malignancy are further broken down into eleven with carcinoma of the cervix and three with carcinoma of the ovary. The diagnosis of cervical malignancy had been made by biopsy. After a course of radiation therapy the uterus was removed and reported as normal. Radical surgery in the properly selected patient, in combination with radiation therapy, is definitely indicated in pelvic malignancy.

Tuberculous Salpingitis.—Previously undiagnosed tuberculous infection was found in four cases at operation, and the uterus was removed with the tubes as a matter of routine. That there was not an associated acid-fast endometritis found in these four cases is merely of academic interest. Certainly there was no way of proving it at operation.

Prolapse.—Vaginal hysterectomy for correction of prolapse in older women is an entirely acceptable procedure. In younger women there is no indication for it, and the Manchester-Fothergill operation or a uterus suspension should be performed instead. There were two patients in this group of twenty-seven cases upon whom hysterectomy should not have been performed. Their ages were 22 and 24 years respectively, and neither had any complaints referable to the uterus other than those produced by the prolapse.

Intractable Bleeding in Older Women.—Of the 28 cases of persistent uterine bleeding, ten were in older multiparas for whom repeated curettements and medical measures had failed to provide relief. Four cases occurred in women past the menopause, making a total of fourteen such cases. In this type patient hysterectomy may be definitely indicated. The authors prefer to employ a small dose of intrauterine radium to check the bleeding without subjecting the patient to a major operation.

2. Conditions which may be considered questionable indications for removal of a normal uterus are:

Inflammatory Disease.—The 110 cases with inflammatory disease of the adnexa are further broken down as follows:

Acute salpingitis	1
Subacute salpingitis	21
Chronic salpingitis	76
Tubo-ovarian abscess	12

Surgery in the acute stages of this disease is definitely not indicated. In the chronic group corrective measures are often necessary. Most of these patients

TABLE I. CONDITIONS FOR WHICH OPERATION WAS PERFORMED.

CONDITION	NO. CASES
Inflammatory disease	110
Endocervicitis	30
Benign ovarian tumors	29
Intractable bleeding	28
Prolapse	27
Lower abdominal pain	20
Endometriosis	17
Pelvic malignancy	14
Cystocele and rectocele	7
Ectopic pregnancy	6
Dysmenorrhea	5
Tuberculous salpingitis	4
Hematoma broad ligament	1
Cholelithiasis	1
No symptoms	1

TABLE II. AGE INCIDENCE.

AGE	NO. CASES
17-20	11
21-30	99
31-40	133
41-50	52
Over 51	5

The average age was 34 years, the youngest, 17, the oldest, 61 years.

are young women, and every effort must be made to preserve their pelvic organs. It has been a common experience of the authors that if operation is delayed long enough in treating salpingitis it will often prove to be unnecessary. The temptation to "clean out" the pelvis in such cases is often strong and must be guarded against. Probably the most difficult decision to make is what to do with the tubo-ovarian abscess at operation. The ovary is usually not identifiable as such, and lies in the inflammatory and scar tissue at the base of the abscess cavity. A satisfactory result can be obtained by resecting the abscess wall and leaving the base of the cavity open and undisturbed. Such cases do not require drainage. Once the continuity of the abscess is broken the reparative processes of the body handle the remaining inflammatory tissue with amazing facility. The uterus should be freed of adhesions and suspended at the same time. The old excuse that if you take out the tubes you might as well take the uterus and ovaries too does not hold water. If the ovaries and uterus are preserved, these patients will continue to menstruate normally.

Endocervicitis.—Of the thirty cases subjected to panhysterectomy for cervicitis, two had an associated dysfunctional bleeding. The remaining twenty-eight presented no symptoms except those referable to the leucorrheal discharge. In the presence of a lesion in the uteruine corpus, cervicitis may be a definite indication for panhysterectomy. In the absence of a lesion in the corpus, it is difficult for the authors to reconcile themselves to the idea that hysterectomy plays any part in the management of cervicitis. Cauterization, conization, and, if necessary, amputation are readily available and simple measures. Even if one feels that metaplasia, epidermization, or the so-called "Bowen's Disease" may be a forerunner of malignancy the simpler measures will just as adequately manage the lesion. In rare instances a questionable lesion is found which cannot be confirmed or denied by biopsy. In such cases the authors prefer careful

observation of the lesion, multiple biopsies, and, if necessary, amputation of the cervix with study by serial section before instituting more radical measures.

Benign Ovarian Tumors.—These thirty cases are further broken down as follows:

Simple serous cyst (Exceeding 5 cm.)	12
Dermoid and teratoma	10
Large benign cystomas	7
Fibroma	1

With a large tumor completely distorting the pelvic structures in an older woman, hysterectomy may be indicated to facilitate the operation. In younger women every effort must be made to preserve the other ovary and the uterus. On occasions, the preservation of a small strip of ovarian tissue on one side only along with the uterus will prevent an artificial menopause. Special attention must be directed to the small follicle cysts and hematomas which result from normal cyclic activity of the ovary. These structures are not abnormalities, yet they are frequently mistaken for pathologic lesions by surgeons and removed. To add the insult of removing a normal uterus to such a procedure should constitute malpractice.

Endometriosis.—In this condition it is the opinion of the authors that removal of a normal uterus or ovaries is not indicated. These patients often do surprisingly well with simple removal of the endometriomata or their partial excision. If necessary, x-ray castration will check the progression of the lesion promptly.

Intractable Bleeding in Young Women.—In these cases hysterectomy represents surrender on the part of the physician to the demands of the patient and her relatives to "do something" to stop the bleeding. This type of case can be most trying to the gynecologist's patience and judgment. In this group falls the youngest patient in this study, a girl 17 years of age.

Hematoma of the Broad Ligament.—This one patient developed a pelvic mass the size of a volleyball subsequent to a curettement. After two months of observation it showed no evidence of subsiding and laparotomy was performed. At operation the pelvic structures were found to be so distorted that hysterectomy was considered advisable.

3. Conditions which are not indication for removal of a normal uterus are:

Lower Abdominal Pain and Dysmenorrhea.—These twenty-five cases are an excellent illustration of what may happen to psychoneurotic women if they pester their doctor long enough. Most psychoneurotics with abdominal complaints manage to get themselves operated upon at least once, but the surgeon who removes more than an appendix in such cases is overzealous, to say the least.

Cystocele and Rectocele.—The seven cases with this complaint alone had no appreciable degree of descensus and no symptoms referable to the uterus. All had a repair of the cystocele and rectocele from below, combined with an abdominal supravaginal hysterectomy. In none was there clear indication for laparotomy, let alone hysterectomy.

Ectopic Pregnancy.—Of these six cases, four were ruptured tubal, one a tubal abortion, and one ruptured ovarian. To add the shock of hysterectomy to a patient already or potentially in shock cannot be considered anything but sheer foolhardiness.

Colelithiasis.—This one case was of a 42-year-old woman whose only complaint was upper abdominal pain produced by gall stones. After cholecystectomy the surgeon thought he detected an enlarged ovary by palpation. He closed

the upper abdominal incision, made a lower abdominal incision, and removed a normal uterus with normal tubes and ovaries.

No Symptoms.—This patient was a 40-year-old woman who reported to a birth control clinic to be fitted with a diaphragm. She had no complaints and her menstural history had always been normal. There was no excess bleeding or discharge. At the clinic she was told by the examining doctor there was a possibility she might have a tumor of the womb and she was referred to a gynecologist. The latter advised the patient that an operation would be necessary. At operation a normal uterus was found and removed.

Conclusions

1. Pelvic malignancy, tuberculous salpingitis, prolapse, and intractable bleeding in older women may be definite indications for removal of a normal uterus.

2. Inflammatory disease, endometriosis, benign ovarian tumors, dysfunctional bleeding in younger women, and endocervicitis are at best questionable indications for removal of a normal uterus.

3. Ectopic pregnancy, cystocele and rectocele per se, psychoneurosis, and dysmenorrhea are not indications for removal of a normal uterus.

4. In this series of 300 operations there was no indication for hysterectomy in 43 cases, or 14 per cent, and questionable indication in 197 cases, or 65.6 per cent.

5. The authors conclude that even in a well-supervised teaching hospital hysterectomies are sometimes performed with little or no justification for the operation.

FURTHER STUDIES IN EARLY PUERPERAL RISING

GORDON ROSENBLUM, M.D., AND EUGENE MELINKOFF, M.D., LOS ANGELES, CALIF.
(From the Cedars of Lebanon Hospital)

IN NOVEMBER, 1945, we reported a series of 582 obstetric patients comprising a study in early puerperal rising,[1] pointing out that this practice goes back to ancient times and is not particularly an outgrowth of the recent shortage of hospital beds. The analyses of our data from that study yielded the following conclusions:

1. Delivered women can safely get up early in the puerperium with no harmful results occurring.
2. Bowel function is improved as a result of early puerperal rising.
3. Early puerperal rising reduces the amount of nursing care required.
4. The majority of patients subjected to early puerperal rising reported favorably on the method.
5. The patients getting up on the third or fourth postpartum day showed no advantages over those patients getting up on the first or second postpartum day.
6. It was our opinion that early puerperal rising resulted in a more rapid and comfortable convalescence, with less asthenia and less postpartum and postoperative depression.

At the time of the above report it was our hope that further study would result. Since that publication appeared, there has been generally a greatly renewed interest in the subject of early surgical and early puerperal rising. There have been many editorials and symposia on the "use and abuse of bed rest" as well as articles in popular magazines which have resulted in a strong public interest in early rising. We have now found that our patients exhibit a far greater knowledge concerning the subject, and we have also noted a definite change in their attitude toward the practice of early rising, whereas previously there was skepticism, there is now eager expectancy. Doctors practicing at the Cedars of Lebanon Hospital who do not allow their patients out of bed early have reported opposition from both their surgical and obstetric patients who believe early rising beneficial. All of this leads to the belief that early puerperal rising is gaining in favor with both the medical profession and the laity.

Method of Study

As in our previous study our cases were divided as follows:

1. Early risers: Ambulatory on the first or second postpartum day.*
2. Intermediate risers: Ambulatory on the third or fourth postpartum day.
3. Late risers: Ambulatory later than the fourth postpartum day.

*At Cedars of Lebanon Hospital, the first postpartum day is defined as "the day following delivery."

Early rising in this series of cases should be defined as controlled ambulation. The patients are encouraged to walk to the bathroom instead of using bed pans, and to remain out of bed for short intervals only. No changes in technique were instituted in any of these patients. Episiotomy repairs were all routinely performed with No. 0000 chromic catgut as described by Waters.[2] Cesarean operations were all performed through low transverse abdominal incisions, except where a previous midline incision existed; the fascia was sewed with double No. 0 chromic catgut suture.

All patients requiring catheterization were catheterized at least one time for residual urine after voiding had begun, and if this amount was above 50 c.c., catheterization was repeated after each voiding until the amount of residual urine was less than 50 c.c. Patients who voided apparently normal amounts of urine without difficulty and at normal intervals were not catheterized at all. The estimations as to the amount of lochia or postpartum bleeding were made from our observation at our daily rounds at the hospital, in addition to the reports of the obstetric nurses in attendance.

Analysis of Statistics

This study is not intended to represent a comparative analysis of the three groups of puerperal women according to their time of rising. As may be seen in Table I, a much higher percentage of cesarean sections fall into the intermediate and the late risers than do in our early risers. This is because any of the patients who were more seriously ill or had more bleeding were not al-

TABLE I. STATISTICS

Total number of cases in series			601	
Total cesarean sections			58	9.6%
Early risers			490	81.6%
Vaginal deliveries	451	92.0%		
Cesarean sections	39	8.0%		
Intermediate risers			93	15.4%
Vaginal deliveries	77	82.8%		
Cesarean sections	16	17.2%		
Late risers			18	3.0%
Vaginal deliveries	15	83.4%		
Cesarean sections	3	16.6%		

TABLE II. BLADDER FUNCTION

Number of patients requiring catheterization after getting up	31
Number of patients not requiring catheterization after getting up	570

	EARLY		INTERMEDIATE		LATE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Number studied	490		93		18	
Number of patients requiring catheterization	167	34.1%	32	34.4%	8	44.4%
Number of patients not requiring catheterization	323	65.9%	61	65.6%	10	55.6%
Total number of catheterizations	435		66		12	
Average number of catheterizations per patient	.88		.71		.66	
Voiding complete on first postpartum day	453	92.4%	87	93.6%	16	88.8%
Voiding not complete on first postpartum day	37	7.6%	6	6.4%	2	11.1%
Clinical urinary infections	11	2.2%	3	3.2%	0	0
Gross morbidity	15	3.0%	7	7.5%	5	27.7%

TABLE III. MISCELLANEOUS OBSERVATIONS

	EARLY		INTERMEDIATE		LATE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Lochia						
normal	485	99%	92	99%	16	89%
excessive	5	1%	1	1%	2	11%
Perineal healing						
good	451	100%	77	100%	15	100%
fair	0		0		0	
poor	0		0		0	
Abdominal wound healing						
good	39	100%	16	100%	3	100%
fair	0		0		0	
poor	0		0		0	
Involution of uterus						
good	483	98.6%	92	99%	17	94.4%
fair	4	.8%	0		0	
poor	3	.6%	1	1%	1	5.6%
Bowel function						
moved spontaneously	88	18%	10	10.7%	1	5.6%
enema required	402	82%	83	89.3%	17	94.4%
Thrombosis	0		0		0	
Embolism	0		0		0	
All other complications						
wound drainage	0	.0	1	1%	0	.0
psychosis	1	.2%	0	.0	0	.0
respiratory infection	1	.2%	0	.0	2	11%
toxemia	2	.4%	2	2%	0	.0
mastitis	1	.2%	1	.0	0	.0
third degree laceration	0	.0	1	1%	0	.0
cystitis	11	2.2%	3	3%	0	.0

TABLE IV. POSTPARTUM STUDIES

	EARLY		INTERMEDIATE		LATE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Number of patients studied	477	100%	88	100%	18	100%
Excessive bleeding during first month post partum	2	.4%	0	0	1	5.5%
Perineal healing						
good	477	100%	88	100%	18	100%
poor	0	0	0	0	0	0
Position of uterus						
anterior	387	81%	70	79.5%	14	77%
mid	31	6.5%	6	6.8%	2	11%
retroverted	59	12.3%	12	13.6%	2	11%

TABLE V. CESAREAN SECTIONS

Number in series	39		16		3	16.6%
Morbidity	3	7.7%	4	25%	2	11.0%
pyelitis	1	2.5%	1	6%	0	0
parametritis	2	5.1%	3	18%	1	5.5%
peritonitis	0	0	0	0	1	5.5%

lowed up as early as the more normal ones. For this reason also the higher morbidity figures in the intermediate and late groups are not significant. However, we feel that it does demonstrate that 490 out of 601 delivered women, or 81 per cent, could be made ambulatory on the first or second postpartum day with obvious benefit.

As in our previous study, we do not feel that the statistics demonstrate any obvious advantage as concerns bladder function. Bowel function seems

definitely improved with many more patients not requiring enemas. Since there were no cases of thromboses or embolism in our total observed series which now comprise 1,183 patients, we are again unable to confirm the reports of other authors that early puerperal and early surgical rising safeguards against these serious accidents. It is notable that we have not had a single case of episiotomy or wound breakdown in our present series of 601, and only one instance of skin separation in our previous series of 582 patients. Our observations do not lead us to believe there is any greater amount of postpartum bleeding, a point mentioned by Hanley.[3]

The postpartum studies reveal that of 721 early risers in our combined series 160 patients, or 22.2 per cent, had a midposition or retroversion of the uterus, while of 244 late risers in our combined series 59, or 24.2 per cent, presented this same finding, not too dissimilar percentages. It appears, therefore, that the belief that early puerperal rising may cause more retroversions of the uterus is unfounded. We have seen no cases of uterine prolapsus in any of our early risers, and we agree entirely with the belief of Guerriero[4] that prolapsus is due to trauma at delivery.

Conclusions

We have presented a series of 601 delivered women, of which 490, or 81 per cent, were made ambulatory on the first or second postpartum day. Together with our previous series of 582 cases, this comprises 1,183 patients studied, of which 737 patients comprise the group of early risers. We believe that our earlier conclusions as enumerated at the beginning of this paper are further substantiated. We believe that the practice of early puerperal rising is gaining favor with the medical profession and with the laity. We intend to continue this practice and believe that time will prove its correctness.

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PRIMARY OVARIAN PREGNANCY

N. Paul Isbell, M.D., and W. Benjamin Bacon, M.D., Brookline, Mass.

(From the Department of Pathology, Harvard Medical School, and The Free Hospital for Women)

PRIMARY ovarian pregnancy occurs approximately once in 25,000 pregnancies.[3] The total number of cases reported has been estimated from forty-four to two hundred.[5, 6] The incidence of its occurrence in ectopic pregnancy is again variously reported from 0.7 to 1.07 per cent.[1-4] If all hemorrhagic lesions of the ovary, such as ruptured follicles, corpora lutea cysts, "chocolate cysts," and hematomas were given routine histologic examination, the number of ovarian pregnancies recognized would be greatly increased.[6, 7] One hundred ten cases of ectopic pregnancy have occurred at the Free Hospital for Women, Brookline, Mass.; of this number the following is the only case thought to be primary in the ovary. Our incidence of this condition is therefore 0.9 per cent.

Mrs. N. M. C., a 24-year-old white housewife, married three years, was perfectly well until March 16, 1946, which was two months before her first visit to the Out-Patient Department and three and one-fourth months before operation; when, after carrying a baby carriage up two flights of stairs, she suddenly felt weak, faint, and dizzy. Shortly afterward she had sudden sharp, severe lower abdominal pain. Palpation of the abdomen by her family doctor, who arrived within the hour, was not painful. Her pain subsided soon and the next day she felt well except for tiredness and a "pulling" sensation in the lower abdomen when she sat erect. That night, she noticed that her navel protruded and was "black and blue," changing to yellow and then resuming its normal color in the course of a week. On the third day she resumed her household duties. She had noted no irregularity or change in character in her menses, her last menstrual period having occurred at its expected time, beginning approximately two weeks before the above episode.

During the next three months, she remained asymptomatic except that on intercourse she occasionally noticed deep pelvic pain never experienced previously. There was also some irregular bleeding consisting of six episodes, the first four at approximately two-week intervals, the last two at three-week intervals; each flow resembling her usual catamenia in duration, amount, and character. These were accompanied by a sense of "fulness" in the pelvis, relieved by the onset of bleeding.

Past medical history was negative except for occasional attacks of "bronchial asthma"; surgical history was negative. The patient had had one child, a full-term, normal delivery, eighteen months prior to entry; there had been no miscarriages.

At her first visit to the Out-Patient Department on May 14, the abdomen was soft, without tenderness or masses; the uterus anterior, small, firm, and movable without pain. The cervix showed a mild circumoral erosion one centimeter in diameter. Deep in the left vault there was felt a tender mass measuring 4 by 5 cm., which was thought to be consistent with a simple cyst. The cervix was biopsied, and she was given an appointment to return in one week. Three weeks later, on June 4, the mass in the left vault was still

palpable, but increased in size to 10 by 12 cm., and was now palpable in the left lower quadrant, 6 centimeters above the symphysis. The mass was somewhat tender.

On June 22 examination under anesthesia confirmed the above findings. The uterus was anterior, consistent with a negative parous, nonpregnant uterus. A smooth, regular, fairly soft, rounded, movable mass approximately 8 cm. in diameter was felt deep in the left vault, which seemed compressible as though it were cystic. The right vault was negative. At a curettage, the uterine cavity was three inches deep, smooth and symmetrical, and yielded a moderate amount of grossly negative endometrium. A laparotomy performed with a preoperative diagnosis of ovarian tumor revealed no blood in the peritoneal cavity. There was, however, one filmy omental adhesion to the left anterolateral parietal peritoneum at which point there was some soft gray-brown material consistent with old blood undergoing organization. A biopsy of this area was taken. The left ovary was enlarged to approximately 7 cm. in diameter, consisting of dark brown hemorrhagic tissue and old blood clot. It was loosely adherent to the posterior parietes of the pelvis. Little or no normal ovarian tissue was left. The right ovary was normal except for a rather large (approximately 2 cm.) corpus luteum, which was biopsied. Both tubes were negative except that the left tube was loosely adherent to the ovarian mass by fibrin and organizing inflammatory exudate. The uterus was consistent with a negative parous nonpregnant uterus.

A left oophorectomy was performed and a grossly negative appendix removed. The patient had an uneventful postoperative course and was discharged on the ninth day. At her six weeks' postoperative visit she had been entirely well, having had an apparently normal catamenia from July 30 to August 4. Pelvic examination was negative.

Pathologic Examination.—Gross: The material consisted of the left ovary, biopsy from right ovary, endometrial curettings, biopsy from left anterior peritoneal wall, and appendix.

The left ovary (Fig. 1) measured 6 by 5 centimeters. The upper portion was dark reddish-brown in color. There were several small dark-colored areas over the rest of the ovary which appeared to be cysts containing old blood. The largest was 1½ centimeters in diameter. There was a denuded area one centimeter wide and two centimeters long across the upper lateral surface of the ovary, one centimeter from the hilum, where the ovary was separated from the left tube. The underlying ovarian stroma was very friable and infiltrated with old and recent hemorrhage. Upon cutting down through this area a thin white membrane was exposed behind which thin bloody fluid could be seen. Upon opening it, it was found to contain an embryo whose crown rump length was 16 millimeters. It was attached to the wall of the cavity by a fusiform cord 4 millimeters in diameter. The fetus showed brownish discoloration and slight maceration of the skin. The lining membrane of the cavity, which was 2½ centimeters in diameter, bulged in on all sides due to the large amount of hemorrhage between it and the surrounding ovarian tissue. Section through the largest of the dark colored raised areas on the surface of the ovary showed it to be a cystic structure filled with organizing blood.

The biopsy from the right ovary had the characteristic thick yellow convoluted wall and hemorrhagic center of a mature corpus luteum.

The biopsy from the left anterior peritoneal wall measured 2 by 3 by 4 millimeters, and was composed of fat and old blood clot.

The endometrial curettings measured 5 by 4 by 7 millimeters.

Microscopic.—Sections from the wall of the left ovary extending into the cavity of the ovisac showed it to be lined with a layer of somewhat flattened cells with deep-staining nuclei and cytoplasm characteristic of the amnion. The

stroma of the amnion was replaced by a wide zone of disintegrating red blood cells scattered among which were a few degenerated cell nuclei and the hyalinized borders of "ghost" villi. Beyond this area there were numerous chorionic villi undergoing various stages of necrosis (Fig. 2). Some were almost entirely hyalinized with a loss of cellular structure, others had undergone fibrosis. A few were seen in which the trophoblast showed only early necrosis and the stroma of the villi contained fetal blood vessels filled with blood. The Hofbauer cells were present in relatively large numbers.

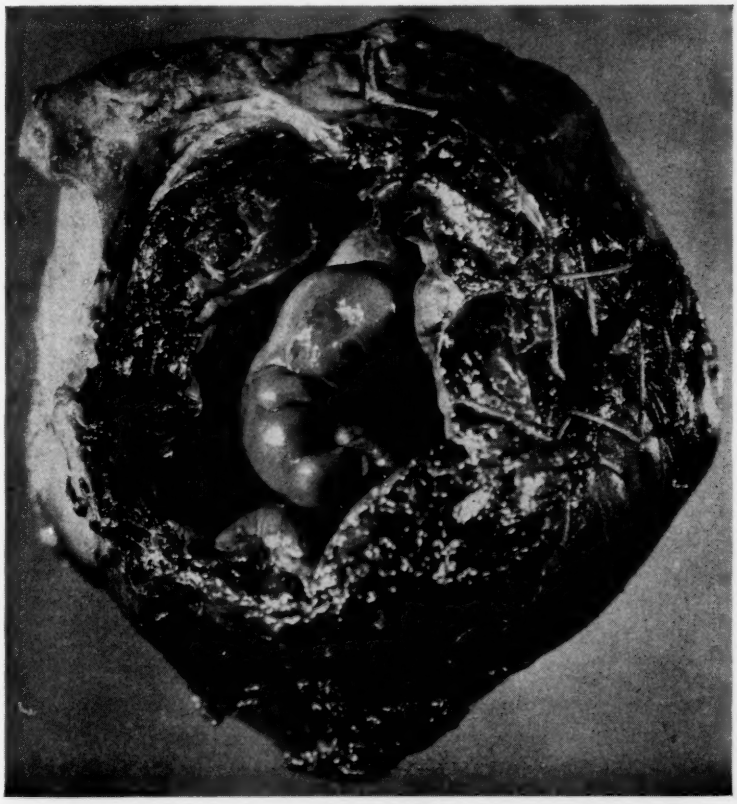

Fig. 1.—The ovary opened to show the embryo and ovisac within the center of the ovary. (Suture material shown was used in closing areas sectioned while trying to locate the corpus luteum of pregnancy.)

Syncytial giant cells showing vacuolization and granular degeneration of both the cytoplasm and nuclei had invaded the ovarian stroma. The latter was heavily infiltrated with red blood cells, round cells, plasma cells, and large macrophages laden with hemosiderin. There were areas containing large pale polygonal cells showing decidual reaction, most of which were showing signs of degeneration. Numerous primordial follicles lined with flattened spindle shape epithelial cells surrounding well preserved ova were seen in the cortex. In early follicles, lined with a more fully developed layer of granulosa cells, the ova had disintegrated. The theca cells of the large atretic follicles had large vesicular nuclei and more abundant cytoplasm simulating a lutein reaction. An old follicular cyst was present whose cavity was filled with degenerated red blood cells and fibroblasts. On the surface of the ovary was a vascularized adhesion which contained an inclusion cyst lined with germinal epi-

thelium, part of which showed beginning degeneration. It was surrounded with a loose, fibroblastic stroma containing large pale nuclei, capillaries, and hemosiderin.

The section from the right ovary showed the cortex to contain many primordial follicles and part of a large corpus luteum (Fig. 3). The central core of the latter consisted of extravasated blood, numerous fibroblasts and some capillaries containing blood. The lutein cells next to the core showed many vacuoles in their cytoplasm. Many of the cells had deep-staining, finely vacuolated cytoplasm with pyknotic nuclei. The capillaries were straight, and most

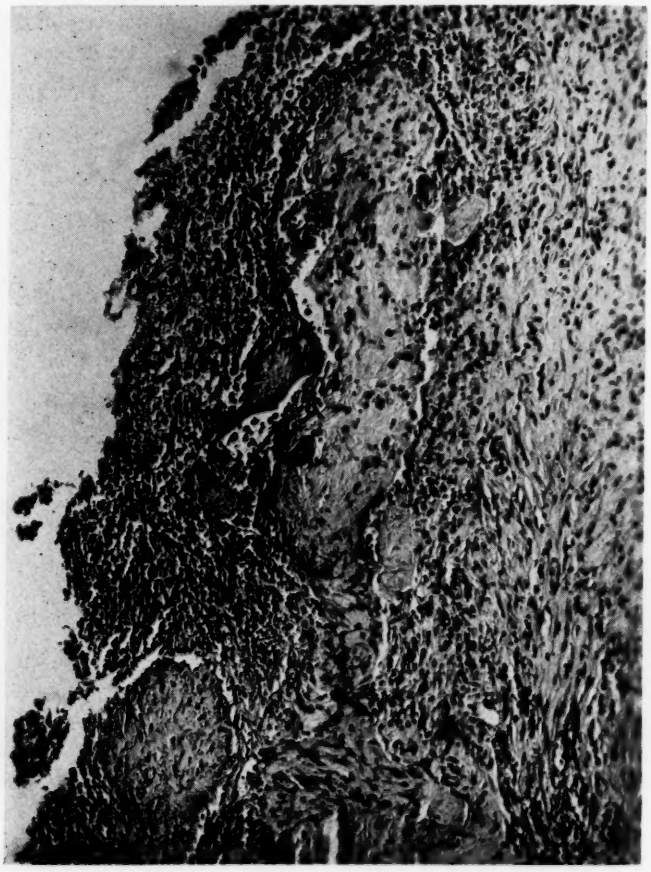

Fig. 2.—Section from inner wall of cavity within the ovary showing invasion of ovarian stroma by chorionic villi and syncytial giant cells.

were collapsed and empty. There was no extravasated blood. There was an abundant supply of blood-filled capillaries in the columns of the theca interna together with a considerable amount of free, pink, granular secretion. The theca interna cells were large and granular, with large vesicular nuclei containing prominent nucleoli and occasional mitoses. The corpus luteum was active and approximately nine days old,[31] which was consistent with the endometrium.

The endometrial curettings (Fig. 4) showed the surface to be undulating and covered with a layer of tall thick columnar cells. The stroma cells immediately beneath the surface and around the spiral arterioles were becoming vesicular and were acquiring more cytoplasm. A few mitoses were seen. The rest of the stroma was loose and moderately edematous. The glands were tortu-

ous and showed slight serration when cut longitudinally. Their epithelium was low columnar with basal ovoid nuclei and no mitoses. The lumina contained small amounts of secretion. The endometrium was secretory type in the twenty-fourth day of the cycle using the critereia set forth by Hertig[32] for diagnosing endometrial biopsies.

The section from the anterior peritoneal wall consisted of a mass of hemosiderin and fibrin in which there were numerous small capillaries, plasma cells, round cells, and fibroblasts.

Fig. 3.—Section of active corpus luteum showing the straight capillaries among the lutein cells and the blood-filled capillaries and free secretion among the cells of the theca interna.

Discussion

The eventual fate of this conception, had it not been removed, is a matter of conjecture. All active growth processes and bleeding had ceased. Organization and resorption were under way, and eventual mumification and lithopedion formation might have occurred, as in the case reported by Norton and Alter.[11]

In many cases, there is often a measure of doubt whether or not the ovary is the primary or secondary site of implantation. However, since both Fallopian tubes were intact and grossly normal, this case is thought to be a primary ovarian pregnancy. It cannot be determined whether or not the ovum

developed in its own follicle or at some other site within the ovary. The corpus luteum of pregnancy had degenerated so much it could not be located by multiple sections of ovary containing the fetus. The biopsy of the only grossly recognizable corpus luteum in the opposite ovary corresponded in age to the current twenty-four day secretory endometrium.

The length of the fetus was consistent with an age of seven weeks according to the tables of Streeter.[8] The vaginal bleeding episodes of the next two months can best be explained on a basis of "teetering" estrogen-progesterone

Fig. 4.—A section of the endometrial curettings showing the beginning predecidual reaction around the spiral arterioles and the dilated secretory glands with moderate serration of the lining epithelium and secretion within the lumina.

hormone levels in the presence of degenerating trophoblast[9]; the latter having finally lost its ability to inhibit the development of a new follicle with subsequent ovulation and the development of a twenty-four day secretory endometrium. It is evident from a review of the reported cases[1-30] that endometrial curettings reveal a wide variation in both proliferative and secretory types, with a decidual reaction present only occasionally. This tends to support Kline's[10] statement that the decidual reaction is not constant and that vaginal bleeding depends on changes other than the casting off of uterine decidua. It has long been known that the uterine curettings are of doubtful value in the diagnosis of extrauterine pregnancy. The etiology of this case, whether due to fertilization of the ovum within its follicle, or subsequent implantation in the same or the other ovary, cannot be stated.

There is no evidence that sterility which is cited by Kuzma and Lillie[12] as a factor, played any part in this case. Endometriosis was not present, which is in contrast to some cases reported by others.[11-14] In view of the almost universal occurrence of endometrial stroma beneath the surface of the ovary which is transformed into pseudodecidua by the stimulus of pregnancy, it is possible that a fertilized ovum which was mechanically delayed in passing to the uterus might cause by its continued proximity to cells originating in the Müllerian system, a sufficient pseudodecidual reaction to encourage implantation and development. Decidua itself is not necessary for implantation or the continuation of a pregnancy.

The authors wish to acknowledge with grateful appreciation the many suggestions and aid given by Dr. A. T. Hertig in the preparation of this report.

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COEXISTENT CARCINOMA AND SARCOMA OF THE UTERUS*

JAMES P. HENNESSY, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, St. Vincent's Hospital)

A TYPE of case which is considered rare is that of coexistent carcinoma and sarcoma of the uterus. According to Newell, only twenty similar cases had been reported prior to 1928—not so long ago. Oscar Frankl reported eight cases which were observed and studied in great detail over a period of fifteen years. He stated that it was possible for both carcinoma and sarcoma to exist in the same uterus, either closely approximated or distinctly apart. He studied the pathology of these tumors very carefully, recognized the fact that an accurate diagnosis was sometimes extremely difficult, and urged that a definite terminology be used in describing them. He suggested that the term sarcoma plus carcinoma be applied to separate tumors, carcinosarcoma to mixed tumors in which sarcoma and carcinoma are intimately mixed, and carcinoma sarcomatodes to a carcinoma which has characteristics of growth of sarcoma.

Virchow applied to all three groups the name carcinoma sarcomatodes, since he considered them to be true mixed tumors in which both epithelium and connective tissue were represented in the neoplastic growth. Herxheimer, in discussing the pathology of sarcoma and carcinoma in the same uterus, suggested three possibilities: (a) that carcinoma and sarcoma may develop simultaneously as the result of the same cause acting in different tissues; (b) that the atypical proliferation of epithelium on the base of a pre-existing sarcoma may lead to the development of a carcinoma within a sarcoma; and (c) that the stroma of a carcinoma may undergo a sarcomatous change. Ewing, in a consideration of the same subject, listed the following possibilities: (a) the simultaneous occurrence of two separate tumors which may invade one another; (b) the development of carcinoma at the point where a submucous or mural sarcoma meets the epithelial layer; and (c) carcinomatous changes in the glands of a sarcomatous or inflammatory polyp.

Most of the cases reported in the literature were either adenocarcinomas of the body and cervix or sarcomas arising from either the endometrium or myometrium, but not sarcomas arising in a myoma. It is obvious that an accurate diagnosis is difficult when the two neoplasms originate in the interior of the uterine cavity and encroach upon each other in such a way that the cells often lose their characteristics.

Carcinoma sarcomatodes of the uterus is the term used to designate a single neoplasm having the morphologic features of both carcinoma and sarcoma. Only seven cases of this type are reported in the literature. Carcinoma sarcomatodes has no characteristic clinical features. It is said to occur mostly in nulliparous patients after the menopause. Bleeding is a constant symptom and appears to be more persistent and profuse than in cases of carcinoma of the fundus of the uterus.

Goldstine reported a case of sarcoma and adenocarcinoma of the body of the uterus and adenocarcinoma of the cervix. The two large masses protruding from the fundus were covered by a markedly thickened endometrium.

*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine at its meeting January 28, 1947.

Microscopically, these tumor masses were large, round, and spindle-cell sarcomas with numerous giant cells. The endometrial covering was typical adenocarcinoma. The myometrium was free from sarcoma; and the adenocarcinoma of the cervix was a separate growth, independent from the carcinoma of the body of the uterus.

Saphir and Vass, in their review of the reported cases of carcinosarcoma, were not convinced that all of them were actually carcinoma and sarcoma. Of the 153 cases which they reviewed, only three or four qualified as multiple neoplastic processes. Of 36 growths occurring in the uterus, they did not believe any to be true coexisting carcinoma and sarcoma. The most common sources of error in interpretation lay in the resemblance to a sarcoma caused by a marked stromal reaction to the invasion of carcinoma, the extreme variability of epithelial cells, especially when transitional or spindle forms were present, and the part played by chronic inflammation in the production of pleomorphic cells resembling sarcoma. Therefore, these authors questioned the coexistence of carcinoma and sarcoma in the great majority of the reported cases.

Hoffman, in his studies, reported a case of myosarcoma and papillary carcinoma of the uterus and believed them to be two separate entities, that is, multiple primary malignant tumors, each having its own histologic characteristics. Since the predominant characteristic of this carcinoma was its papillary arrangement without any surrounding fibrosis, there was little reason to interpret the separate sarcoma as an extreme fibroblastic reaction to the carcinoma. Likewise, there was no inflammatory change which might serve as a cause of extreme fibroblastic reaction.

Barnes reported two cases in which two independent primary growths were demonstrated. In neither case was there definite evidence that the sarcoma had arisen on the basis of malignant fibroid degeneration. On the contrary, there was a distinct topographic separation of the two tumors in the uterus.

In a case of sarcocarcinoma of the uterus, reported by Jaffe, the author believed that the carcinoma caused the sarcomatous degeneration of the stroma. He did not think it a common stroma which reacted against the irritation by the carcinoma; the tendency for its excessive growth was already present, and the carcinoma merely enhanced this state. In the portio of the uterus there was the disposition to malignant new formation in both the epithelium and the mesenchyme. The first to become manifest was the carcinoma, which in turn caused the appearance of the sarcoma.

A case of carcinoma and sarcoma in the same uterus was described by Watson. Since both ovaries were involved, a complete hysterectomy with removal of the adnexa was performed. Examination showed a typical adenocarcinoma of the endometrium and beneath it, but completely separated from it, an area of abnormal tissue that would be classified as sarcoma because of its histologic characteristics. The ovarian mass on the right side showed typical adenocarcinoma, whereas that on the left side displayed characteristics of sarcoma rather than of carcinoma. Because of this unusual condition Watson stated that it was an open question whether his case should be called one of carcinoma and sarcoma in the same uterus or whether it should be classified as "carcinoma with a bizarre type of anaplasia."

Case Report

A case from my own experience is that of Mrs. R. B., a widow, white, 55 years old. A previous diagnostic curettage resulted in a diagnosis of adenocarcinoma of the corpus. She was admitted to the hospital on Nov. 2, 1943, with a

history of leucorrhea and spotting for the past three years. For the last three months she had been passing clots. She has lost 20 pounds during the past six months. She had no pain, but complained of a feeling of exhaustion.

Her past history was essentially negative. She had had two full-term children, delivered normally, and one spontaneous miscarriage at eight weeks. Meno-

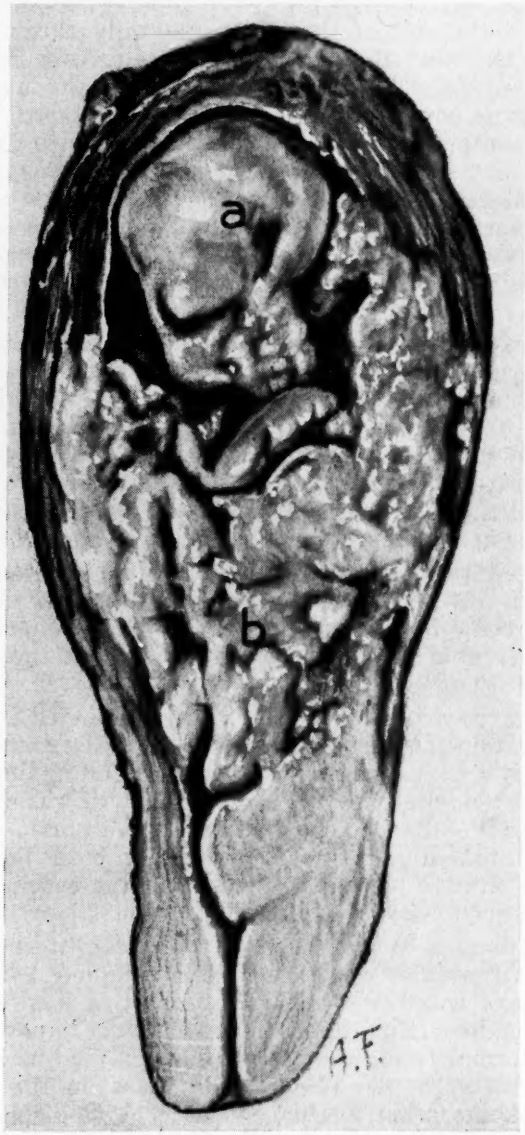

Fig. 1.—Gross specimen showing (*A*) sarcoma, (*B*) adenocarcinoma.

pause occurred at the age of 51 years. She had always been in good health until the appearance of the first of the above noted symptoms three years ago.

Physical examination showed a well-developed woman, weighing 116½ pounds. Her temperature, pulse, and respiration were normal, as were her heart and lungs. Her blood pressure was 160/92; hemoglobin, 78 per cent. Vaginal examination revealed a good parous pelvic floor. The cervix was

clean and smooth. The uterus was slightly enlarged, regular in shape, mobile, and in fairly good position. No lesions were found in the adenxa.

Operation.—When the abdomen was opened, no adhesions were found. The uterus was somewhat enlarged, slightly globular, and symmetrical. The adnexa were atrophic. A complete hysterectomy was done, including removal of the tubes, ovaries, and a moderate cuff of vagina. Except for a moderate staphylococcus infection of the abdominal wound, her postoperative course was uneventful.

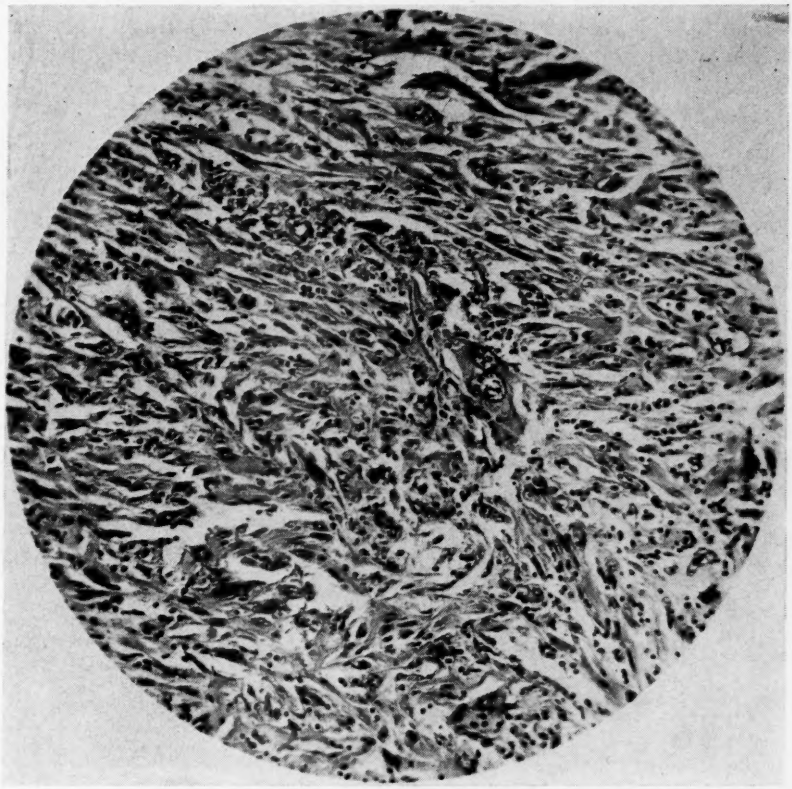

Fig. 2.—Sarcoma of uterus. Note profusion of spindle cells together with scattered giant cells. (×110.)

Pathologic Examination.—The specimen consisted of a uterus including the cervical portion with both tubes and ovaries attached. The uterus was slightly enlarged, weighing 110 Gm. and measuring 9 cm. by 4 cm. by 5 cm. When the uterus was sectioned, an irregular gray, solid, friable tumor was revealed, filling and distending the endometrial cavity and replacing the entire endometrium. The tumor penetrated the myometrium in some areas. In general, the myometrium was thin. The tubes and ovaries appeared atrophic.

Microscopic Examination.—The bulk of the tumor was a typical cylindrical cell adenocarcinoma with well-formed glands lined by tall columnar cells. Sections prepared from the fundal portion of the tumor (Fig. 1*A*) showed it to be sarcoma. It was composed chiefly of interlacing bundles of plump spindle cells. Many of the cells were anaplastic; few were large, bizarre, giant in size.

Diagnosis.—Adenocarcinoma and sarcoma of the uterus.

Follow-Up.—The patient reported for a follow-up examination six months later, at which time she stated that she felt well and had no complaints. She had gained 9½ pounds; hemoglobin was 82 per cent. Examination showed the vaginal vault to be clean and well suspended. No tenderness or thickening was noted in the pelvis. She was seen six months after that; and, although she had lost six pounds, she said that she felt well and was going to business regularly. The pelvic findings were the same as those of the previous visit. She was seen on Nov. 2, 1945. She still felt well and had no complaints. Her weight was 119 pounds; hemoglobin, 78 per cent. Urine examination gave negative results. There was no change in the pelvic findings. She stated she remained well until March 24, 1946, when she was operated upon by Dr. Robert

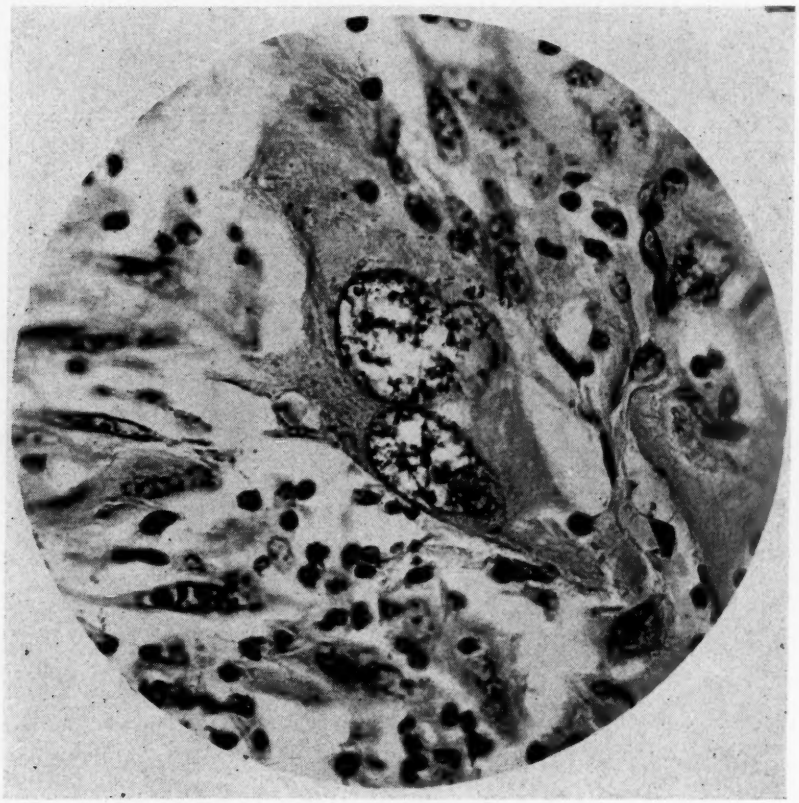

Fig. 3.—Sarcoma of uterus. Picture shows large bizarre giant cell with two nuclei of unequal size. (×450.)

Moseley of Kingston, N. Y., for strangulated right femoral hernia. The badly damaged loop of small intestine could not be delivered through the femoral ring, so a laparotomy was done. An adenocarcinoma, primary in the ilium, was found about three inches proximal to the strangulated loop. The tumor was firmly adherent to the lower abdominal scar, and there was extensive involvement of the mesenteric and retroperitoneal glands at the base of the mesentery. There was no palpable liver metastases. The hernia was repaired, and a wide resection of the ilium was done with a side-to-side anastomosis. The glands could not be removed. She received a course of radiation therapy (3,000 RU) at the Memorial Hospital. On June 28, 1946, she was symptom

free, had gained weight, and there was no palpable mass in the abdomen. She was last seen Dec. 13, 1946, and stated that she had no complaints and had gone into business for herself. Her weight was 118 pounds; hemoglobin, 60 per cent. Pelvic findings were the same as of previous visits.

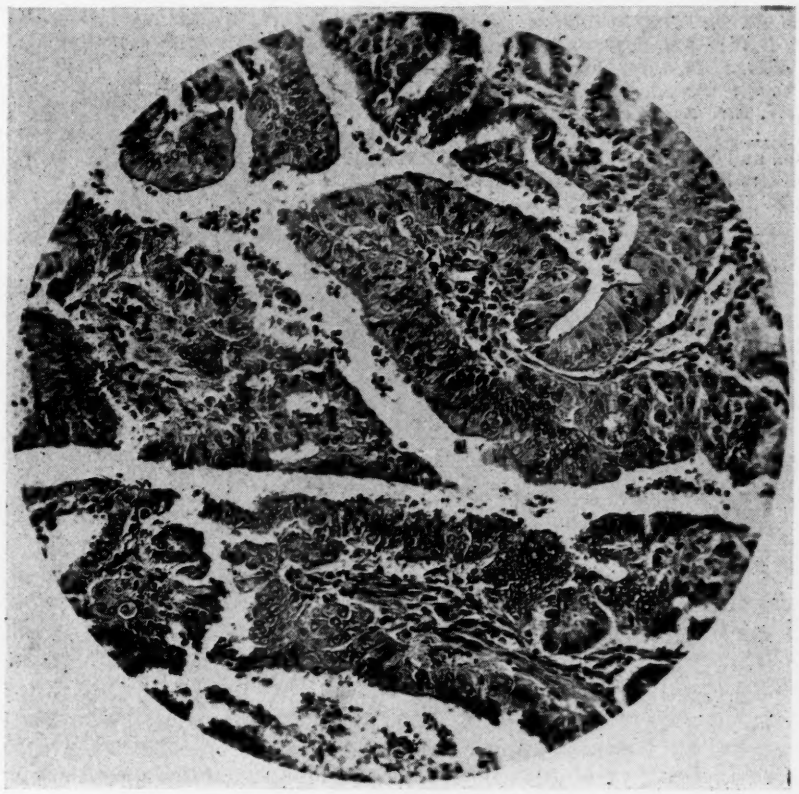

Fig. 4.—Carcinoma. Note cylindrical cell adenocarcinoma. (Hematoxylin-eosin stain, ×110.)

Summary

1. The coexistence in the same uterus of two tumors, one an adenocarcinoma and the other a sarcoma, is rare, only about 28 cases having been reported.

2. A review of the literature on the existence of carcinoma and sarcoma in the same uterus revealed considerable confusion in terminology. Many tumors are composed of irregular and nondifferentiated cells, which make the origin difficult to determine. This difficulty has led to much confusion in the nomenclature and to the introduction of a great many unnecessary names. As new light is thrown on their origin, there is no doubt that many pathologic conditions now considered sarcoma will be classified as separate types of malignancy.

3. A case of coexistent adenocarcinoma and sarcoma of the uterus is presented in the hope that it may be of some little help in the subsequent classification of these tumors.

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CARCINOMA OF THE CERVIX PRIMARILY DIAGNOSED BY THE STAINED VAGINAL SPREAD*

ROBERT E. SEIBELS, M.D., F.A.C.S., COLUMBIA, S. C.

FROM the gynecologist's viewpoint, the early diagnosis of carcinoma of the reproductive organs is the principal objective of the physical examination of women at stated intervals, annual or semiannual. As long as the physician had to rely on historical, tactile, and visual sources for evidence of neoplastic change, he was constantly aware of the limitations inherent in diagnosis and prognosis, based on these procedures. With the advent of stained spreads of vaginal secretions, a study of their cytology opened up whole new fields. Through these studies he becomes familiar with endocrine changes and activities and variations in therapeutic responses within reasonably definite limits. In suspected cancer cases, the value of these studies has been too frequently attested to need repetition.

Advantages that these spreads present are that they may be made as frequently as the curiosity of the examiner dictates, are inexpensive to carry out, and present no inconvenience or danger to the patient. That these spreads have the weight of a biopsy is not suggested. However, when the cytologist finds cells of suspicious appearance he is then induced to make further studies and to keep the patient under careful observation at frequent intervals. With recurrence of malignant appearing cells, a biopsy then is indicated. In addition, he must follow his biopsy into the pathologic department and insist on sectioning of the entire block. The importance of this is emphasized below.

Carcinoma of the cervix and fundus in the early or preinvasive stages presents the greatest challenge for prompt recognition and, at the same time, offers the greatest chance for complete cure with the least surgical risk. With these considerations in mind, we have for the past two years practiced the study of stained cytologic spreads as just as regular a part of the examination of the patient as examinations of the blood, urine, and other routine laboratory procedures. The extraordinary value such studies may have is illustrated by the following case report.

This married, white patient, aged 38 years, reported for annual physical checkup on Dec. 12, 1945. Her periods had been perfectly regular until November 5, when her menstrual flow began on the expected date and lasted as usual for four days. Following this, there was a discharge of mucus occasionally tinged with blood and associated with some backache. The bleeding was increased by housework and occurred once or twice following coitus. The discharge had never been sufficient to require wearing a pad. There were no associated symptoms except for an increased frequency of urination for a few days from November 29. There had been one pregnancy, eighteen years before, with a rather difficult delivery, and the cervix and perineum were repaired in 1936.

The physical examination was entirely negative, with a hemoglobin of 90 per cent and a weight of 120 pounds (as usual). The abdomen was relaxed and no tenderness or masses were palpable. Cervix was rather pale, somewhat irregular, resembling a cervix that had had a plastic repair. Just within

*Presented at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Greensboro, North Carolina, February 15 to 16, 1946.

the cervical canal about 9 o'clock, there was an area which was a rather flannel red and which bled when suction was exerted on it to secure a spread. The cervix was firm but not hard, felt somewhat irregular. The uterus was small, in good position, easily movable; the fornices were negative. Movement of the cervix was slightly painful as was pressure on the uterosacral ligaments, but there was no limitation of movement of the cervix. Perineum was well healed, no cystocele, no rectocele.

Spreads of the secretion from the vagina and cervical canal were made and these were stained by a modification of the Papanicolaou stain. In addition to many leucocytes and blood, cells consistent with a diagnosis of epidermoid carcinoma were found. This finding was confirmed by two other laboratories. Repeated smears were made of cervical and vaginal secretions and all showed irregularly shaped cervical cells with marked heteroplasia (Fig. 1). On January 5, a wedge-shaped piece corresponding to the reddened portion of the cervical canal was removed for microscopic study. Sections from this material varied from practically normal with a small amount of round cell infiltration to definite Grade II squamous cell carcinoma of the cervix with invasion of the cervical mucosa, some areas exhibiting attempts at pearl formation.

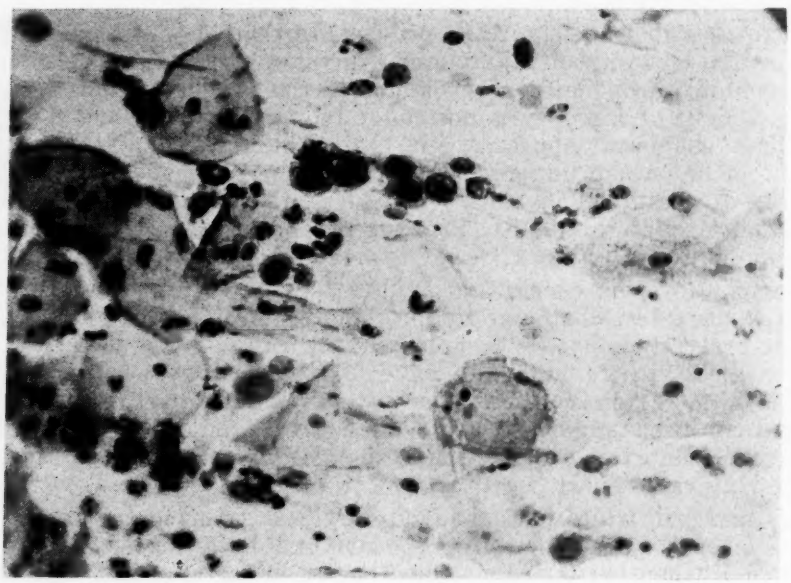

Fig. 1.—Stained vaginal spread. Note malignant cells in upper center.

On Jan. 28, 1946, the uterus, tubes, and ovaries were removed with a ¾ inch cuff of vagina by abdominal operation.

Macroscopic examination revealed an ulcer 1 cm. from the external os measuring 2 cm. by 1 cm. On section there was a growth in the cervix 1 cm. in depth, definitely confined to the cervical canal and, while it extended down into, it did not penetrate through the cervical tissue, there being 5 mm. of apparently uninvaded tissue external to it.

Sections from the cervix revealed infiltration of an epithelial malignant tumor. The tumor was growing in the form of broad flat bands and long fingerlike processes with occasional groups of isolated cells. These cells were quite large with variations in shape and with large, sharply defined hyper-

chromatic nuclei, with occasional mitoses (Figs. 2 and 3). (The microphotographs do not show with sufficient clarity what is dramatically apparent in the microscope—the absolutely identical appearance of the cells in the spreads with those seen in the tissue sections.)

Microscopic Diagnosis.—Squamous epithelioma of the cervix, grade II.

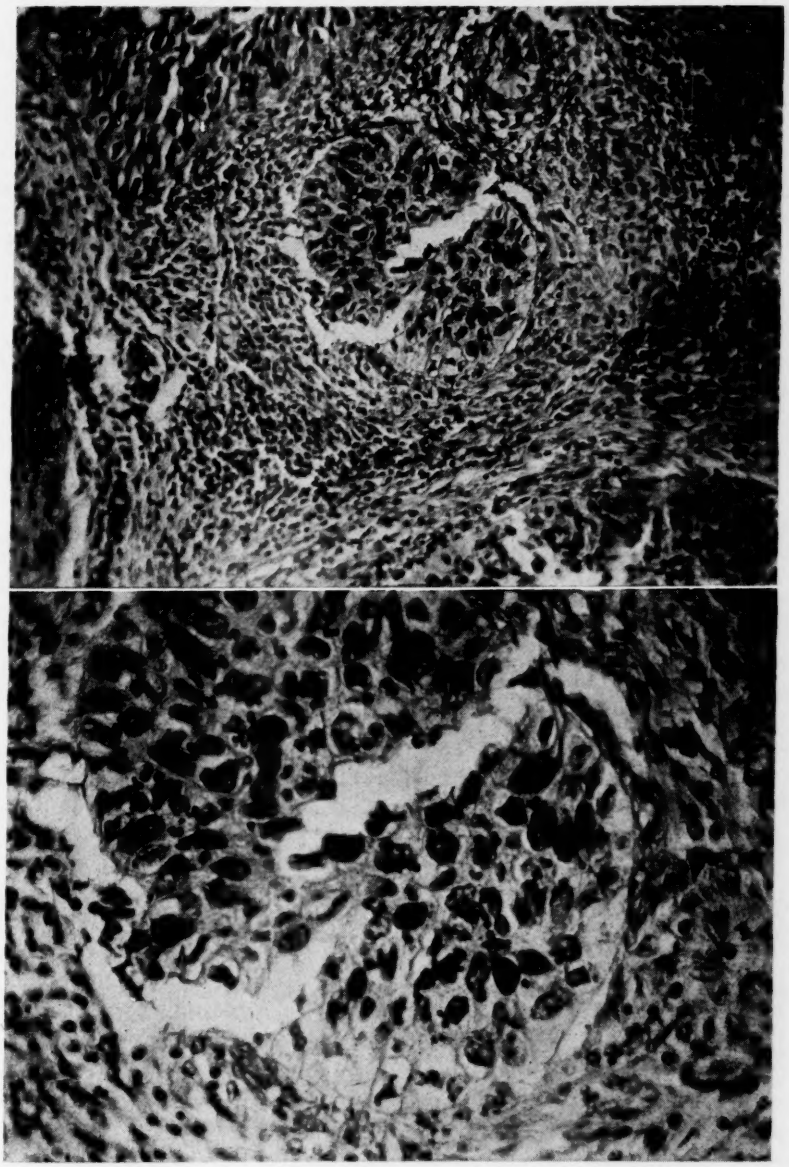

Fig. 2.—Photomicrograph (low power) operative specimen.
Fig. 3.—Photomicrograph (high power). Note resemblance of cells to those in Fig. 1.

Comment

It is to be emphasized that this patient did not come in because of the reddish discharge, as this history was obtained only on careful questioning. She had been in the habit of a "November examination" for five years, and it had been delayed by changing her residence to this city.

While the history given by this patient is perfectly consistent with that associated with early neoplastic change, and in the light of subsequent findings, one is impressed with the story of bleeding associated with trauma, such a history is daily recorded in women of the fourth decade in the absence of malignancy. This reassuring fact, taken with the reluctance of the clinician to do a biopsy or a diagnostic curettage, often accounts for the average delay of nearly seven months between the first visit of the patient and her receiving definitive treatment. It has been estimated that delay in the presence of carcinoma decreases the chance of cure by 3 to 4 per cent per week. In this individual cells were found which two independent observers confirmed as consistent with undoubted squamous cell carcinoma. These findings certainly impelled a biopsy which, without their discovery, might easily have been delayed to the serious depreciation of the hope of operative cure. As in the case reported by Ayre, the first cuttings were entirely negative for cancer and exhibited only inflammatory changes. A less zealous laboratory, and without the cytologic findings, might have failed to make the further sections which revealed carcinomatous findings.

False positive diagnoses of carcinoma from vaginal spreads will probably be made by the unwary and have been reported by those who may be considered experts. An error of 2.9 per cent in "negative called positive" occurred in a series of 861 cases reported by Meigs. A conservative attitude must be maintained when such findings are the sole basis for the diagnosis of uterine carcinoma. However, Papanicolaou and others have reported such cases in which positive cells were found with no clinical supportive evidence which, within six months, have been confirmed by curettage or biopsy.

False negative reports are the peril of the uninitiated and may represent insufficient study by the most adept. Thus Meigs shows an error of 10.3 per cent in 1,015 cases, of which 154 were shown to have cancer on microscopic section. Sixteen spreads of these proved patients were negative: 7 of the 16, on review of the slides, showed cancer cells and were missed because every field was not examined. There is thus a corrected error of 5.7 in false negatives in this report.

From these studies we may assume an expectation of 95 per cent correct in both positive and negative reports—an error which may be expected to diminish with further experience.

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CONGENITAL HYDRONEPHROSIS

LIEUTENANT MICHAEL L. ALLEGRETTI, MEDICAL CORPS, UNITED STATES NAVY
(From the U. S. Naval Hospital, U. S. Training Center, Great Lakes, Ill.)

RECENTLY Potter reorted 20 cases of congenital renal agenesis all of which were remarkable because of the presence of a peculiar facial appearance and hypoplasia of the lungs. One hundred forty cases have been previously reported. In addition to the peculiar facial appearance and hypoplasia of the lungs, all of the cases showed skeletal anomalies. These anomalies were most apparent in the lower extremities. All of the cases showed a complete absence of renal tissue, including the absence of both ureters.

Our case of congenital hydronephrosis is interesting, because it simulates the cases mentioned above in every respect except for the fact that both kidneys were present. However, there was considerable atrophy of renal parenchyma due to a bilateral congenital hydronephrosis. We feel that this resulting renal insufficiency is enough to bring about the changes mentioned above, and that a complete renal agenesis need not be present.

The infant's mother was a 23-year-old, white, para i, gravida ii. Her first pregnancy had terminated spontaneously at eight months. A 7-pound male was delivered who had a cleft palate, and lived only eight hours. No postmortem examination was made. Three weeks before her expected date of confinement with her second pregnancy, the mother entered the hospital because of vaginal bleeding. Her pregnancy had been normal for eight months with no signs of pre-eclampsia, acute exanthem, or fetal abnormality. Admission examination revealed a soft cervix dilated 1 cm., and moderate bleeding from the cervical os. The blood pressure was 104/64. The fetal heart was easily heard to be regular at a normal rate. The labor lasted twelve hours, and the mother received $\frac{1}{150}$ grain of scopolamine followed by N_2O and ether inhalation anesthetic during the second and third stages. The baby was resuscitated with moderate difficulty. Shortly after birth, he became cyanotic intermittently and survived only seven and one-half hours. The maternal and paternal family histories were noncontributory. The mother was Kahn negative and Rh positive. At necropsy the pertinent findings were as follows:

The body for examination was that of a small male infant having a crown rump measurement of 28 cm. Several gross abnormalities were obvious. The head was normal in size, but the sagittal suture was separated 0.5 cm. throughout its length. There was a moderate amount of fine black hair on the head. The ears arose from the head at points lower than the level of the eyes, approximately opposite the level of the mouth. The bridge of the nose was convex in its sagittal plane with no concavity at its upper end, and sharp and flat at the tip. The tongue was bifid and short. From the right facial area a 0.75 cm. tongue of lymphoid-like tissue protruded into the oral cavity. There was a small cleft in the palate involving mainly the uvula about 0.5 cm. in length. The line of fusion of the palate was accentuated and extended as a furrow through the alveolar ridge. The mandible was 1.5 to 2 cm. shortened from the angle to the mentum so that the chin was markedly receding. The upper extremities were grossly normal except for the hands. The thumbs were short, curved medially under the second digits which were long, and straight. The lateral three digits of both hands curved medially under the second digit. The

thorax was normal except for flaring of the left costal margin. The umbilical cord had been tied and cut recently. The anus was patent. The genitals appeared normal for a male infant. Both testes were palpable in the inguinal canal. The lower extremities were grossly normal except for the feet. There was a lateral displacement of both feet on the lower end of the tibias and fibulas, giving the feet a varus deformity. The feet were broad and flat. The lateral three digits of both feet were webbed and curved medially. The medial digit of each foot was short and curved laterally, while the second digits were long and straight. The lungs weighed 30 grams. The right lung was grossly normal. The left lung was a deeper bluish red. Cut section was not remarkable. Both lungs floated. The adrenals together weighed 8 grams. They were normal in size, shape, and consistency, and on cut section. The kidneys were grossly abnormal. The right kidney was 3.5 cm. in length, weighed 20 Gm. and felt cystic. On cut surface the calyces were large cystic structures obliterating all but a thin margin of cortex. The left kidney was 2.0 cm. in length and weighed only 10 grams. The surface was studded with small subcapsular, thin-walled cysts which were distended with urine. On cut surface more dilated calyces were apparent. The ureters were very tortuous, dilated, and thickened, but no obstruction could be demonstrated. The bladder was normal in size, shape, and position. There was marked congestion of the mucosa of the bladder.

Microscopic examination revealed the lungs to be congested and atelectatic, but there was no marked hypoplasia. The kidneys were made up of large calyces lined with transitional epithelium, which in some areas extended to within a few millimeters of the renal capsule. The glomeruli show diffuse hyaline degeneration in varying stages similar to a picture of subacute glomerulonephritis. There was interstitial fibrosis with tubular atrophy. One area of the bladder showed marked submucosal hemorrhage.

In summary, our case seemed to be one of congenital hydronephrosis, diffuse hyaline change in the glomeruli, and bilateral tortuous ureters. Secondary to the hydronephrosis and glomerular degeneration there was interstitial fibrosis, tubular atrophy, resulting in a diminution of normal kidney tissue. The lungs were atelectatic and showed only a slight tendency to hypoplasia. There were multiple deformities of the osteocartilaginous structures.

Our case would indicate that intact renal physiology is necessary to the normal development of osteocartilaginous structures. Renal agenesis is merely one form of renal insufficiency in utero, and this case demonstrates a second.

Special Article

THE CINCINNATI OBSTETRICAL SOCIETY, SEVENTIETH ANNIVERSARY; AN HISTORICAL NOTE

ARTHUR G. KING, M.D., CINCINNATI, OHIO

SEVENTY years ago the most recent advance in the field of obstetrics and gynecology was Emmett's trachelorrhaphy and the surgical repair of the perineum. The hydrostatic bag was unknown and Dührssen was yet to propose his incision of the cervix. The first uterine suspension had not yet been done, and the streptococcus was unknown. The Porro technique of hysterectomy had just been announced as a lifesaving measure in cesarean section, and it was to be five years before Saenger proved the value of suturing the uterus during the operation. Only 108 cesarean sections had been done in the United States, and the mortality was 59 per cent. Although a successful abdominal delivery had been performed in 1827 in neighboring Newtown, Ohio, it was to be two years before the first cesarean section was done in Cincinnati.

Refulgent in the inspiration and tradition of Dr. Daniel Drake, Cincinnati, a city of 230,000, had about 600 doctors in practice. There were three medical schools: The Medical College of Ohio, The Miami Medical College, and the College of Medicine and Surgery. Three medical journals were published regularly: *The Lancet-Observer, The Clinic,* and *The Cincinnati Medical Journal.* And there were two general medical organizations: The Academy of Medicine, and a dissident group called The Cincinnati Medical Society, a name used as far back as 1819.

The first organization in the United States devoted to obstetrics and gynecology was the Obstetrical Society of Boston, formed in 1861. In 1864 the New York Obstetrical Society was started, and in 1868, the Obstetrical Society of Philadelphia. The fourth city in the United States to have a group of doctors meeting for "the promotion of knowledge in all that pertains to Obstetrics and Diseases peculiar to Women" was Cincinnati. In 1876, Thaddeus A. Reamy formed the Cincinnati Obstetrical Society, and it has been in active continuous existence ever since. Starting with eleven members, a total of one hundred thirty names are on the roster, including Reamy and J. W. Underhill, who were among the first men elected to the American Gynecological Society, founded the same year, Giles S. Mitchell, one of the founders of the American Association of Obstetricians and Gynecologists, and E. B. Stevens, editor of the *Cincinnati Obstetrical Gazette.*

For a number of years after the founding of the society, the complete transactions were published in the *American Journal of Obstetrics and Diseases of Women and Children* started only eight before. Many of the early papers represented great advances in gynecologic thinking and described procedures which for the time were very radical. The early minutes reveal vigorous discussion and trenchant criticism, and often the extemporaneous remarks were longer and better documented than the essays. Although it is amusing to read of a serious advocacy of the use of leeches to reduce congestion in a hyper-

trophic cervix during a long labor, it is stimulating to learn that Marmaduke Burr Wright insisted, in 1876, that "no man is justified in using forceps with an undilated os." Apparently his teaching at the time was a minority protest against current practice. The handling of incomplete abortion was as moot a question then as it is today; Stevens led one faction of doctors with the motto of "Time, Rest, and Laudanum," while Zinke captained the other with the statement: "No woman is safe till the uterus is empty." Throughout the years the papers presented at the society meetings, critically discussed, have been the basis for some important contributions to the professional literature of the country. The seventieth anniversary celebration of the founding of the Cincinnati Obstetrical Society is a milestone in the steady progress that has been made in the practice of obstetrics and gynecology, and is a token of enthusiam for continued effort.

Editorials

The Need of a Knowledge of Medical Genetics

THE recent observance of the 100th anniversary of the New York Academy of Medicine highlighted anew a problem which has been too long neglected, but which is growing rapidly in importance and cannot be stressed too strongly. The need for a thorough training of medical students in the principles and practical applications of medical genetics is becoming more apparent with each new discovery in the field.

At this gathering Dr. H. J. Muller, who received the Nobel Prize in Medicine for 1946, discussed the question of the accumulation of mutations in human populations, both from natural causes and from artificial radiation, including x-rays and the emanations from nuclear fission such as those used in the atomic bomb. He presented valuable suggestions for "mutational prophylaxis."

Dr. Laurence H. Snyder of the Ohio State University, in 1940, in the Biggs Lecture on Medical Genetics and Public Health, then discussed the training of physicians in this field. He pointed out that the adequate understanding of Dr. Muller's important presentation, which has a bearing on the lives of all of us, is dependent upon a knowledge of the basic principles of heredity. Furthermore, the physician needs not only a basic acquaintance with genetics, but a specialized knowledge of medical genetics, because of the very practical benefits which this may bring to the practice of medicine.

Dr. Madge T. Macklin has for years stressed at every opportunity the need for medical genetics in the medical curriculum. At first only a voice crying out in the wilderness, she has been joined by a veritable chorus. The researches of Landsteiner, Levine, Wiener, Snyder, Wilson, Schweitzer, Neel, Allan, Cotterman, Penrose, Haldane, and a host of others have unearthed material of great importance to the physician, but requiring a knowledge of medical genetics to be adequately understood. The applications of these researches in diagnosis, in preventive medicine, in genetic prognosis, and in forensic medicine are too important to be neglected any longer.

Medical schools are slowly but surely responding to this challenge. Fifteen years ago Macklin conducted a survey which revealed the fact that not a single medical school at that time offered a course in medical genetics, and only two schools presented any material on the subject in other courses. Snyder has also presented the results of a similar survey just completed. Today three medical schools have required courses in medical genetics, four have elective courses, and ten more are planning to present such courses in the near future.

In addition, forty-two medical schools actively present material on medical genetics in connection with didactic or clinical courses.

This progress is highly commendable, but much remains to be done. Every premedical student should be required to take a course in the principles of genetics, and every medical student should have training in medical genetics and its practical applications. Only then will the remarkable strides in this medically important science be made functional and profitable. To those engaged in obstetric practice, these facts are of particular import.

An International Congress of Obstetrics and Gynecology

IT WOULD appear appropriate to continue the holding of international congresses in this important field of medicine at definite intervals. The year 1947 marked the Bicentenary of the Rotunda Hospital which afforded an opportunity, while commemorating the founding of a great and well-known institution, to develop a gathering of obstetricians and gynecologists from many ports of the world. The program of this meeting held during the past July disclosed a representation from 14 different countries and was largely devoted to obstetric topics including the history of midwifery, puerperal sepsis, eclampsia, shock in obstetrics, sterility, fetal and neonatal mortality.

The desirability of bringing together the workers and practitioners in the domain of this branch of medicine is one of paramount importance, for an exchange of ideas is a contributing factor to progress. The great war has disrupted such gatherings but the advent of peace, even if this is not attained as rapidly as one might wish and hope for, nevertheless should bring about a resumption of relations between professional men of the world as soon as possible. Thought, therefore, may be given to the possibility of holding another congress in the near future, say in 1950, and preferably in the United States, where none has ever been held. We would suggest a city in the Eastern seaboard, large and readily accessible, such as New York, with its extensive hospital facilities, an abundance of hotel accommodations and many other attractions. The active promoting agency for the purpose might well be the American Committee on Maternal Welfare which has developed a machinery for such purposes, as evidenced by the two previously held national congresses. It would seem desirable that steps be taken at an early date to organize the project so that invitations might go forth to participate in the program by countries, institutions, and individuals, and the necessary support developed by our various organizations devoted to the specialty. The United States, because of its many advances in medicine, and its well-developed interest in obstetrics and gynecology, would be the logical host to develop an international gathering of this nature.

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Physiology, Etc.

Harjola, Oiva: Contribution on the Knowledge of the Peripheral Blood Picture During Pregnancy and the So-Called Anemias of Pregnancy, Acta obst. et gynec. Scandinav. 26: 1-130, Supplement 3, 1946.

Harjola, of Helsinki, considers in great detail the peripheral blood pictures among 220 women subjects divided into the following four groups, 16 nonpregnant normal women; 82 normal and pregnant women; 71 pregnant cases exhibiting an anemia, as determined by Sahli hemoglobin values between 60 to 69 per cent; and, 51 cases of pregnant subjects, each having a Sahli hemoglobin less than 60 per cent.

The author finds that the color indices of the pregnant normal woman compare favorably with those of the normal nonpregnant women, save in certain factors of difference which occur in the former during the latter part of their antepartum period. At this time the reticulocytes increase 35 per cent; leucocytosis occurs late; the neutrophilic leucocytes show a shift to the left (younger forms in the smear), and the serum iron values are increased. Pregnancy does not influence the diameter of the erythrocytes or cause anisocytosis. The cell volumes and saturations are likewise not affected by pregnancy.

In the group of milder anemias in pregnancy the writer observes these more significant conclusions—when the hemoglobin decreases, the red cell count decreases at the same time, but the color index remains constant; as the new red cells develop, the reticulocytes increase to an average of 13 per cent; the drop in hemoglobin value causes no effect upon the mean cellular diameter of the erythrocytes, but the anisocytosis increases by 14 per cent. As the hemoglobin decreases, a hyposideremia develops in about one-third of the cases which evidenced a decrease in serum iron.

In the group of more serious anemias of pregnancy, among that series having a Sahli hemoglobin value less than 60 per cent, the writer concludes with these more significant findings—as the hemoglobin falls the number of erythrocytes and their color indices markedly drop in all cases; reticulocyte response show increases in more than 50 per cent of the cases; there is a gradual increase in the neutrophilic leucocyte count, and a shift to the left with each successive month of pregnancy; anisocytosis increases on an average of 18 per cent, and the mean of the serum iron value drops to 51 per cent, as compared to those pregnant and in good health. The author concludes that gastric acidity exerts no decisive influence upon the development of anemias even among those cases exhibiting the more serious states during their pregnancies.

The monographic article is excellently documented with many tables, figures and detailed collateral minor conclusions. C. E. FOLSOME.

Vara, Paavo, and Halminen, Eero: On Fetal Electrocardiography, Acta obst. et gynec. Scandinav. 26: 249-262, 1946.

The authors, reporting from the Second Women's Clinic and First Medical Clinic of Helsinki University, proposed six questions they hoped to answer anent the application of

electrocardiography to several states of pregnancy. These investigators attached a twenty-power amplifying tube in front of a small model Siemens electrocardiograph. They obtained their best results using abdominal applications, one electrode being applied above the symphysis and another on either side of the fundus. In the cases of early pregnancy (third and fourth month of pregnancy) only two electrodes were used, the one a lead disc on the end of an insulated rod placed against the portio, and the other immediately above the symphysis pubes. After a long period of studying more trustworthy methods, 30 cases of pregnancy, in different stages, were submitted to electrocardiography; viz.: five cases during the tenth month, 11 cases in the ninth, four in the eighth, three in the seventh, two in the sixth, three in the fifth, two in the fourth, and one in the third month. Positive results were obtained in 29 cases, and negative in the thirtieth case pregnant five months. An induction of labor produced a dead and macerated fetus.

The writers conclude: (1) with the aid of an electrocardiogram it is possible to determine quickly whether the fetus is alive or dead, (2) the electrocardiogram is useful in early pregnancy diagnosis, (3) the fetal heart rate could be proved independent of the maternal heart rate, (4) the electrocardiogram was of no value in determination of the presentation, position or attitude of the fetus, and (5) the fetal heart action disorders, excluding arrhythmias could not be diagnosed by this method. The article is well illustrated with electrocardiographic reproductions. C. E. FOLSOME.

Vilter, Carl F., Morgan, Dorcas, and Spies, Tom D.: Nutrition in Pregnancy. The Effects of Dietary Deficiency in Pregnancy and the Detection and Treatment of Nutritional Deficiency Diseases, Surg., Gynec. & Obst. **83:** 561, 1946.

This paper presents a short but concise review of some of the current literature on nutrition in pregnancy. The study herein briefly discussed is one in which 229 mothers between the ages of 18 and 45 years who were patients at the Nutrition Clinic in Birmingham, Alabama, were considered in relation to deficiency diseases. Only 4 of the 229 mothers had definite symptoms of nutritional disease prior to the first pregnancy. However, 135 developed symptoms during lactation or pregnancy, and the symptoms appeared to be more frequent during the last trimester. Methods of prevention of nutritional deficiencies are presented, and means of diagnosis are described. The authors state that the principles of treatment for nutritional disease occurring in pregnancy do not differ from those in the nonpregnant woman. A high caloric, high protein diet with adequate vitamins and minerals is recommended by the authors. L. M. HELLMAN.

Misrahy, Georges A.: The Metabolism of Histamine and Adenylic Compounds in the Embryo, Am. J. Physiol. **147:** 462-470, 1946.

Misrahy, University of Cairo, Egypt, using two separate batches of about 200 eggs each, traced the development of histamine and adenosine, two of the most powerful vasodilator substances among the body "metabolites," throughout the hatching period. It was ascertained as a preliminary to this study that nonfertilized eggs were completely free of these substances.

The author was able to demonstrate that the production of these two substances ran approximately parallel to the growth of the embryo, save that the peak increase of histamine was delayed by two to three days as compared to adenosine. He discusses and compares organ distribution of these two active agents in the embryo and the adult. The metabolism of histamine and adenosine was similar in the chick and rat embryos, and considers these two substances are the result of metabolic processes in the embryo itself and are not supplied through the placenta in a ready-made form.

These observations in this basic study, well documented with two figures and four tables, will be of much interest to obstetricians interested in the relationship of these compounds to human pregnancy and some of its obstetric accidents. C. E. FOLSOME.

Pregnancy, Complications, Etc.

Clerc, J. P.: A Consideration on Manual Removal of the Placenta and Its Puerperal Morbidity, Gynaecologia **121:** 213-220, 1946.

Clerc, of the Obstetric Clinic of Geneva, describes the results following manual removal of the placenta in 100 cases representing 1.4 per cent of the total 6,973 deliveries at that institution, from 1940 to 1944.

The author used the technique described by Killian and Schanta, and also by Knaus. After disinfection with antiseptics, the gloved hand is introduced into the uterine cavity and brought along the line of cleavage of the placenta and the uterine wall. The placenta is separated gradually and permitted to slide down the forearm. The intrauterine hand is kept in the uterus until contractions decrease its size. Every effort is made to avoid reintroduction of the hand. The manual removal is followed by a hot intrauterine irrigation, 50° C., with or without the preliminary injection of Basergine (an ergot preparation). When the return flow is clear tincture of iodine is added to the irrigant; later the iodized water is replaced by a two per cent solution of Desogene. The patient is given then a prophylactic dosage of sulfonamides (Uliron, Dagenan, or Cibazol).

The writer states that manual removal of the placenta should be performed only as a last resort; that "Basergin" should be given intravenously before the operation and strict asepsis observed.

Clerc found their morbidity low; 75 of the cases did not develop fever, while in 11 cases fever of low degree occurred sometimes following transfusions. In 12 cases complications such as thrombophlebitis, pulmonary embolism, abscesses and puerperal fever were seen. The two fatalities were ascribed to other causes—severe toxemia and syphilis in one patient, and the second patient died following embryotomy after a neglected shoulder presentation discovered eight days after rupture of the membranes of acute peritonitis.

The lapsed time between rupture of the membranes and manual removal of the placenta was 0 to 10 hours in ten of the febrile and 57 of the afebrile and 14 of the afebrile; twenty-five to forty-eight hours in three cases in each the febrile and afebrile groups; forty-nine to seventy-two hours in one febrile case and more than seventy-two hours in three of the febrile and one of the afebrile cases. In other words, 72 per cent of the 25 febrile cases had placental removal twenty-four hours or less since the rupture of the bag of waters, as compared to 95.25 per cent of the afebrile series in the same period of time. C. E. FOLSOME.

Aycock, W. Lloyd: Acute Poliomyelitis in Pregnancy. Its Occurrence According to the Month of Pregnancy and Sex of Fetus, New England J. Med. **235:** 160, 1946.

The author reports 236 cases in which the month of pregnancy in which the disease occurred is known, and nine cases in which it occurred from two to twenty-three days after delivery.

Available statistics suggest that pregnancy predisposes to acute poliomyelitis, and that there is a tendency for the disease to occur in the first trimester in women who are carrying a male fetus, and in the third trimester in those who are carrying a female fetus.

JAMES P. MARR.

Redell, Gunnar: Parathyroprival Tetany and Pregnancy, Acta obst. et gynec. Scandinav. **26:** 1-10, 1946.

Redell, of Falun, from his own personal observation and three others collected from Gothenburg, Stockholm, and Norrkopings, stresses the importance of serum calcium determination in women becoming pregnant who have given previous histories of postoperative tetany. The author emphasizes that Borcher's pessimistic attitude and management of parathyroprival tetany in pregnancy, and often quoted in the scanty literature, is too radical. He concludes that these cases should have better diagnostic care, more frequent antepartum

observations, and the physician should be prepared to combat acute signs of tetany and deliver the patient in the hospital. The author does not discuss therapy, his objective being principally to suggest that there is no cause for alarm or radical treatment when this condition is found in pregnancy. C. E. FOLSOME.

Radiation

Ritala, A. M.: Clinical Investigations of the Complication of Rectovaginal Fistula Following Radium Therapy of Cervical Carcinoma, Acta obst. et gynec. Scandinav. **26**: 193-224, 1946.

Ritala, impressed by observation of a rectovaginal fistula developing as a complication following radium and x-ray therapy for cervical cancer that had "two fingers" of thickening in the left parametrium, decided to evaluate the cancer of the cervix cases, grades I and II, which had received radiation therapy. Excluding the surgical cases; and those without adequate follow-up, the writer considered 160 comparable grades I and II cervix carcinoma, all of which had received "Stockhold method" of radiation therapy. Follow-up and correspondence with 90 of these patients exhibited no rectal symptoms; but 70 patients, 42 per cent, suffered more or less severe rectal symptoms after radium therapy—seven cases having rectovaginal fistula and one case rectovaginal and vesicovaginal fistula.

The rectovaginal fistulas occurred six to thirteen months, on the average eleven months, after radium treatment. The average weight loss was 10 kilograms. In the eight cases of rectal perforation, the average radium dosage used was 5,600 mg. hr. in the vagina and 3,300 mg. hr. in the uterus—*exceeding* by 2,000 mg. hr. the Stockholm Method—and on an average 1,100 mg. hr. excess in the vaginal dose. Ritala stresses that the method of application of radium in this series was wrong because the lead screens, though loose and thin, were not used at all in these specific cases, as was the custom in usual cases. He stresses this point by stating—"proper training of the physician in gynecological radiation therapy as well as the use of the surgical knife is a requisite."

The writer seems little concerned about the associated roentgen therapy; cases 1 and 2 received totals of 2,000 r; cases 4, 5, and 8, a total each of 6,000 to 7,000 r; case 6, the dose in Helsingfors Contard technique; and case 7 an exceptionally large dose of 18,000 r, of which 9,000 r was given after the fistula appeared.

The author concludes by stressing the role of the traumatic cumulative effect of overdosage of radium in producing rectovaginal fistula in grades I and II cancer of cervix. He outlines in considerable detail the value of proper physician training in the management of radium therapy, and individualization of the case reporting for treatment of what are termed "early carcinoma" grade I or II. C. E. FOLSOME.

Sterility, Fertility, Contraceptives, Etc.

Leonard, Samuel L., Perlman, Preston L., and Kurzrock, Raphael: A Turbidometric Method for Determining Hyaluronidase in Semen and Tissue Extracts, Endocrinology **39**: 261-269, 1946.

The authors adopted the turbidometric method of Kass and Seastone for determining hyaluronidase for assaying the enzyme in semen and tissue. They report the activity in *turbidity-reducing units.*

Differences in properties of bull and human semen necessitated some modifications in preparation of the material for assay. Assays of single samples from human semen are reported. These results indicated a wide variation in the relationship between the sperm count and the enzyme concentration. C. E. FOLSOME.

Mann, T.: Studies on the Metabolism of Semen. III. Fructose as a Normal Constituent of Seminal Plasma. Site of Formation and Function of Fructose in Semen, Biochemical J. 40: 481-491, 1946.

Mann, of Molteno Institute, Cambridge University, one of the foremost authorities on biochemistry of the semen, provides in this article most valuable documented information on the basic research concerned with reducible carbohydrate content of seminal plasma. He has established that, contrary to the views generally held, it was found that the reducing carbohydrate of the seminal plasma is not glucose but d (-)-fructose. This sugar has been purified from the seminal plasma and identified by its reducing value, optical activity, preparation of the methylphenyl-fructosazone, yeast fermentation tests, and other methods.

Mann found that fructose accounted for practically the whole of the yeast-fermentable reducing sugar in the seminal fluids of bull, ram, rabbit, boar, and human seminal plasmas. He was able to demonstrate little, if any, glucose in these specimens from the above species.

The author observed that the fructose level varied from one species to another, and even within the same species there were individual differences—providing clinicians with another possible clue in the evaluation of relative male infertility on the basis of hypo-fructose levels in the seminal plasma. In the bull, the highest levels were found: 1.0 Gm. fructose per 100 ml. seminal plasma.

Sperm obtained directly from the epididymis contained scarcely any fructose. This sugar is acquired by the semen from the accessory glands, principally the seminal vesicles. In certain animals not possessing these structures, notably the rabbit, the prostate was found rich in fructose.

C. E. FOLSOME.

Mann, T.: Studies on the Metabolism of Semen. III. Fructose as a Normal Constituent of Seminal Plasma. Site of Formation and Function of Fructose in Semen, Biochem. J. 40: 481-491, 1946.

The chief function of fructose in semen is to supply the spermatozoa with readily glycolyzable material. Stored seminal specimens show a progressive fall in the content of fructose and an accumulation of lactic acid.

The author concludes that normal spermatozoa utilize fructose, as this is the chief sugar available in seminal plasma, but their enzymic equipment enables them to metabolize equally efficiently glucose and mannose. The breakdown of these three sugars in sperm is initiated by a hexokinase interaction with adenosinetriphosphate. The subsequent metabolic degradation is through diphosphohexose, phosphotriose, phosphoglyceric acid, to pyruvic acid to lactic acid.

It is to be noted that Mann found the rate of fructolysis in semen was highly dependent on temperature. At 5° to 10° C. storage, an appreciable proportion of seminal fructose still remains after forty-eight hours' incubation, but at 30° to 37° C. the disappearance of fructose is only a matter of a few hours. Twelve excellently arranged tables document Mann's article.

C. E. FOLSOME.

MacLeod, John, and Summerson, William H.: The Phosphatase Activity of Human Spermatozoa, J. Biol. Chem. 165: 533-539, 1946.

The authors, at Cornell, aware that oxidation reactions in the sperm cell were secondary to those of sugar breakdown (glycolysis) determined to study the possibility of phosphate transfer as it might be of major significance to the metabolic processes in the cell. They investigated the metabolism of human spermatozoa in the presence of phosphate esters known to be of significance in carbohydrate metabolism in other tissues. Using washed sperm cells and evaluating with Warburg techniques they determined the effect of spermatozoa on adenosine triphosphate, adenylic acid (yeast and muscle), the various hexose mono- and diphosphates, Beta glycerophosphate and acetyl phosphate. While human spermatozoa did hydrolyze adenosine triphosphate to produce adenylic acid, other phosphate esters of recognized significance were not hydrolyzed under the same condition. In the former the hydrolysis did not modify the production of lactic acid from glucose by the cells. The liberation of phosphorous from the adenosine triphosphate was not accompanied by phosphate transfer, nor was any energy yielded by this reaction made available for the maintenance of motility.

C. E. FOLSOME.

Items

American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held in Pittsburgh, Pennsylvania, from June 1 to June 7, 1947, at which time two hundred fifty candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months, regardless of the duration of the course.

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948, at 2:00 P.M.

Applications are now being received for the 1948 examinations. Closing date for these applications will be Nov. 1, 1947.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

Diplomates certified by the American Board of Obstetrics and Gynecology on June 7, 1947:

ANGELL, JOSEPH S., 715 Lake Street, Oak Park, Illinois
ARMSTRONG, JOHN T., 4115 Fannin Street, Houston 4, Texas
BABA, GEORGE R., 3521 North Fremont Street, Chicago 13, Illinois
BACHTEL, MAY B., 2418 Travis Street, Houston, Texas
BAKEN, MELVIN P., 1009 Nicollet Avenue, Minneapolis 2, Minnesota
BAKER, DAVID M., 1130 Morrison Street, S. W., Portland, Oregon
BANNER, EDWARD A., Mayo Clinic, Rochester, Minnesota
BARKER, ROBERT H., 1101 Beacon Street, Brookline, Massachusetts
BAUM, HUGO C., 55 East Washington Street, Chicago 2, Illinois
BERNICK, ELI A., 104 South Michigan Avenue, Chicago 3, Illinois
BIEREN, ROLAND E., 749 Upsal Street, S. E., Washington 20, D. C.
BIRCH, WILLIAM G., 420 John Street, Kalamazoo, Michigan
BISHOP, EDWARD H., 255 South Seventeenth Street, Philadelphia 3, Pennsylvania
BORTNICK, ARTHUR R., 634 North Grand Boulevard, St. Louis, Missouri
BRACK, CHARLES B., 11 East Chase Street, Baltimore 2, Maryland
BRADBURN, GEORGE B., 720 North Michigan Avenue, Chicago 11, Illinois
BROWN, GERALD F., 322 DeMers Avenue, Grand Forks, North Dakota
BUNKIN, IRVING A., 1165 Park Avenue, New York 28, New York
CALLAHAN, EDWARD T., 200 Rutgers Street, Rochester 7, New York
CALVIN, GEORGE F., 439 Thirtieth Street, Oakland 9, California
CARIKER, MILDRED, Mayo Clinic, Rochester, Minnesota
CHANDLER, EDWIN A., 4611 Caroline Street, Houston 4, Texas
CLANCY, JOHN, 730 Broadway, Seattle 22, Washington
CONTI, VINCENT S., 86-43 One Hundred Fifth Street, Richmond Hill 18, Long Island, New York
COOPERMAN, NORMAN R., 116 South Michigan Avenue, Chicago 3, Illinois
CRAWLEY, LAWRENCE Q., 101 East Eighty-ninth Street, New York 28, New York
CROOKS, PHILIP E., 124 Main Street, Johnstown, Pennsylvania
CROSS, JOHN B., 312 Medical Arts Building, Atlanta, Georgia
CROWELL, JAMES A., 412 North Church Street, Charlotte 2, North Carolina
CULINER, ALEXANDER, Two Austin Crescent, Toronto, Canada
CUNNINGHAM, JOHN R., One West Seventieth Street, New York City, New York
DALEY, EDMUND F., 1835 Eye Street, N. W., Washington 6, D. C.
DALY, ROBERT F., 188 East State Street, Columbus 15, Ohio

DANFORTH, DAVID N., 720 North Michigan Avenue, Chicago, Illinois
DARNER, CHARLES B., 807 Broadway, Fargo, North Dakota
DECKER, ALBERT, 10 West Seventy-Fourth Street, New York City, New York
DERIEUX, GEORGE H., 1302 Medico-Dental Building, San Diego 1, California
DIENNA, NICHOLAS P. A., 1811 South Broad Street, Philadelphia, Pennsylvania
DIGGS, EVERETT S., 11 East Chase Street, Baltimore 2, Maryland
DILLON, WALTER F., 7449 Cottage Grove Avenue, Chicago 19, Illinois
DORGAN, LEWIS T., United States Naval Hospital, San Diego 34, California
DORMAN, DANIEL B., 74 North Street, Pittsfield, Massachusetts
DOWSETT, JACK W., 410 Medical Arts Building, Portland, Oregon
DUCKMAN, SIMON, 904 Bushwick Avenue, Brooklyn, New York
EARLY, LLOYD S., 9400 Euclid Avenue, Cleveland, Ohio
EDGELOW, ARTHUR F. G., 76 Maple Street, Springfield, Massachusetts
EGAN, JOSEPH F., 319-321 Main Street, La Crosse, Wisconsin
ELIA, ANDREW D., 362 Commonwealth Avenue, Boston, Massachusetts
ENO, LAUREL S., 313 David Whitney Building, Detroit 26, Michigan
FANDRICH, THEODORE S., 1067 Fisher Building, Detroit 2, Michigan
FELD, DAVID, 738 Maccabees Building, Detroit 2, Michigan
FINN, JOSEPH L., 7109 Rising Sun Avenue, Philadelphia 11, Pennsylvania
Fiorino, John F., 708 Medical Dental Building, Everett, Washington
FREDERICK, LEWIS O., 423 Third National Building, Dayton 2, Ohio
FREE, HARRY W., 952 Fisher Building, Detroit 2, Michigan
FREEMAN, PERRIN N., 474 Main Street, Greenfield, Massachusetts
FRENCH, RICHARD L., 4789 Vineland Avenue, North Hollywood, California
FRENCH, TRAVIS A., 332 Union Trust Building, New Castle, Pennsylvania
FRY, CHLOE O., 131 State Street, Harrisburg, Pennsylvania
GAGE, WALTER P., 64 East Eighty-Sixth Street, New York 28, New York
GARLINGHOUSE, RICHARD E., 723 Sharp Building, Lincoln, Nebraska
GERONDALE, ELMOND J., 750-751 Fisher Building, Detroit, Michigan
GILETTO, BASIL J., 1441 Tasker Street, Philadelphia, Pennsylvania
GILLESPIE, J. P., 1011 Forrest Avenue, Gadsden, Alabama
GILLESPIE, LUKE, 1180 Beacon Street, Brookline, Massachusetts
GLENNER, ROBERT J., 3837 Broadway, Chicago 13, Illinois
GOLDMARK, CARL (JR.), 1097 Madison Avenue, New York 28, New York
GOLDSMITH, JOSEPH W. (JR.), 1774 Hartford Avenue, St. Paul 5, Minnesota
GOLDSTEIN, LOUIS B., 450 Sutter Street, San Francisco, California
GOODHAND, CHARLES L., 1130 Market Street, Parkersburg, West Virginia
GORMAN, WILLIAM A., 2000 Van Ness Avenue, San Francisco 9, California
GRACE, HELEN K., 6107 North Marshall Street, Philadelphia 20, Pennsylvania
GRAHAM, THEODORE K., 279 Park Avenue, Paterson 1, New Jersey
GREENBERG, AARON E., 395 Ocean Avenue, Brooklyn, New York
GREENE, GEORGE G., 109 Esplanade, Lexington 9, Kentucky
GREENE, LEON N., 135 Central Park, West, New York, New York
GREENE, RONALD R., 720 North Michigan Avenue, Chicago 11, Illinois
GREENTREE, LEONARD B., 1669 Eddington Road, Cleveland Heights 18, Ohio
GRIER, JOHN J., 107 South Seventeenth Street, Omaha, Nebraska
GRIFFIN, EUGENE L., 1282 South Oxford Road, N. E., Atlanta, Georgia
GRIMES, WILLIAM H. (JR.), 1259 Clifton Road, N. E., Atlanta, Georgia
GROSS, JOSEPH, 10465 Carnegie Avenue, Cleveland, Ohio
GRUSETZ, MATTHEW W., 960 Sterling Place, Brooklyn, New York
HALLATT, JACK G., Permanente Foundation Hospital, Oakland, California
HANNON, THEODORE R., 1215 Walker Avenue, Houston 2, Texas
HARTMAN, WILLIAM F., 139 East Walnut Street, Lancaster, Pennsylvania
HEALEY, EDWARD F., 101 B Street, San Rafael, California
HEINRICH, JEROME F., 1046 Wilson Avenue, Chicago 40, Illinois
HENDRICKS, CHARLES S., 1433 Twelfth Avenue, Altoona, Pennsylvania
HENGERER, ARTHUR, 425 State Street, Albany, New York
HESKETT, BYFORD F., Eight South Michigan Avenue, Chicago, Illinois
HEYL, W. MEREDITH, 100 West Coulter Street, Philadelphia 44, Pennsylvania
HIGH, RALPH L., 201 Wheeling Street, Apartment Six, Muncie, Indiana
HOENIG, ROBERT B., 146 Central Park, West, New York 23, New York
HOFFMAN, EDWIN S., 766 Fisher Building, Detroit 2, Michigan.
HOFFMAN, GEORGE L. (JR.), 133 South Thirty-Sixth Street, Philadelphia 4, Pennsylvania
HOFMEISTER, FREDERICK J., 425 East Wisconsin Avenue, Milwaukee 2, Wisconsin
HOVIS, WILLIAM F. (JR.), 425 East Wisconsin Avenue, Milwaukee 2, Wisconsin
HUBER, ERWIN T., 1119-21 Missouri Theatre Building, St. Louis 3, Missouri
HUGHES, EMMA, Washington Sanitarium and Hospital, Takoma Park 12, Maryland
HUGHES, JOHN C., 121 University Place, Pittsburgh, Pennsylvania
HUGHES, PARKER K., 1208 Bankers Trust Building, Des Moines 9, Iowa

ISBELL, N. PAUL, 2945 East Kentucky Avenue, Denver, Colorado
JANUARY, DERICK A., 179 Allyn Street, Hartford, Connecticut
JENKINS, HARRY H., 514 West Church Avenue, Knoxville, Tennessee
JOHNSON, C. GORDON, 210 Baronne Street, New Orleans, Louisiana
JONES, JOHN H., 837 Boston Building, Salt Lake City 1, Utah
JONES, RICHARD L., Professional Center, Glencove Avenue, Box 886, Glen Head, Long Island, New York
JONES, WARREN E., Medico-Dental Building, Sacramento, California
KASDON, S. CHARLES, 127 Bay State Road, Boston 15, Massachusetts
KAUFMAN, MORTON S., 1835 Eye Street, N. W., Washington, D. C.
KELLY, ALOYSIUS T., 1300 Cornaga Avenue, Far Rockaway, Long Island, New York
KERR, RICHARD K., 209 South Nevada Avenue, Colorado Springs, Colorado
KILROE, JOHN C., 45 East Sixty-Second Street, New York 21, New York
KINGSLEY, DUDLEY J., 121 Cameron Street, Sarnia, Ontario, Canada
KIRKENDALL, HENRY L., 74 Front Street, Worcester, Massachusetts
KIRTZ, LOUIS, 4952 Maryland Avenue, St. Louis, Missouri
KOLODNY, SYDNEY M., 1224 Roosevelt Building, 727 West Seventh Street, Los Angeles 14, California
KOPANS, DAVID E., 311 Commonwealth Avenue, Boston 15, Massachusetts
KREBS, JOSEPH M., 634 North Grand Avenue, St. Louis 3, Missouri
KREMBS, M. ALEX, 425 East Wisconsin Avenue, Milwaukee 2, Wisconsin
KRISS, BRUNO R., 49 East Ninety-Sixth Street, New York 28, New York
KRUMBHAAR, G. DOUGLAS, 321 Dartmouth Street, Boston, Massachusetts
LADY, WILLIAM T., 800 Alabama Avenue, S. E., Washington, D. C.
LAIRD, MARION D., 21 East Eighty-seventh Street, New York 28, New York
LANGSTON, WILLIAM G., 725 North Glasgow Drive, Dallas, Texas
LAPP, WARREN A., 686 East Thirty-Seventh Street, Brooklyn 3, New York
LAUSTER, CARL F., 2065 Adelbert Road, Cleveland, Ohio
LAUTERBACH, CHESTER H., 277 Alexander Street, Rochester, New York
LAVEN, MAX B., 10515 Carnegie Avenue, Cleveland, Ohio
LAWRENCE, GEORGE J. (JR.), 40-27 Murray Street, Flushing, New York
LEHMANN, BENJAMIN J., 311 South Second Street, Hamilton, Ohio
LEONARD, THOMAS M., Gallinger Municipal Hospital, Washington, D. C.
LIVINGSTON, SEYMOUR H., 910 Park Place, Brooklyn 16, New York
LOEWINTHAN, LAWRENCE, 505 West End Avenue, New York, 24, New York
LORING, ROBERT E. L., Four Chestnut Street, Springfield 5, Massachusetts
MACER, GEORGE A., 71 Glen Summer Road, Pasadena, California
MANLEY, JAMES S., 542 County Street, New Bedford, Massachusetts
MAREK, CHARLES B., 605 Medical Arts Building, Baltimore 1, Maryland
MATTHEWS, HARRY C., 507 Building and Loan Building, Saginaw, Michigan
MCCALL, MILTON L., 1814 Spruce Street, Philadelphia, Pennsylvania
MCCLURE, ROBERT W., 1306 David Whitney Building, Detroit 9, Michigan
MCCORMICK, CHARLES O. (JR.), 26 East Ohio Street, Room 621, Indianapolis 4, Indiana
MCDOWELL, JAMES F., 2167 Highland Avenue, Birmingham, Alabama
MCGILL, FRANCIS X., 41-31 Seventy-Sixth Street, Jackson Heights, Long Island, New York
MEILING, RICHARD L., 2205 East Broad Street, Columbus, Ohio
MIER, THOMAS M., 4500 Olive Street, St. Louis 8, Missouri
MILLER, IRVIN, 650 Main Street, New Rochelle, New York
MILLER, KARL L., 1101 David Whitney Building, Detroit, Michigan
MILLER, ROLLIS R., 3100 Market Street, Youngstown 7, Ohio
MITCHELL, MANCEL T., 1409 Willow Street, Minneapolis 4, Minnesota
MITCHELL, ROBERT MCNAIR, 330 South Ninth Street, Philadelphia 7, Pa.
MOHAN, JOHN Q., 210 West Ninth Street, Cincinnati 2, Ohio
MORRISON, FRANK A., 205 West Third Street, Alton, Illinois
NARDONE, ANTHONY A., 1511 Tasker Street, Philadelphia 45, Pennsylvania
NEILSON, DUNCAN R., 225 Mayer Building, Portland 5, Oregon
NEILSON, RONALD P., 225 Mayer Building, Portland 5, Oregon
NELSON, EDWARD W., 1407 South Carrollton Avenue, New Orleans, Louisiana
NOLAN, JAMES F., 630 South Kingshighway, St. Louis 10, Missouri
NORTHWAY, FREDERICK J., 490 Post Street, San Francisco 2, California
NOVAK, WALTER S., 313½ Huron Avenue, Port Huron, Michigan
OGBURN, LUNDIE C., O'Hanlon Building, Winston-Salem 3, North Carolina
OLDHAM, WILLIAM E., 842 Barret Avenue at Breckenridge, Louisville 4, Kentucky
OTT, HAROLD A., 706 Maccabees Building, Detroit 2, Michigan
PEARL, SARAH A., 365 North San Vincente Boulevard, Los Angeles 36, California
PEARSON, JED W. (JR.), 1834 K Street, N. W., Washington, D. C.
PENICK, GRIDER, 15 North Robinson, Oklahoma City, Oklahoma

PETERSON, PAUL G., 1315 East Forty-Seventh Street, Seattle 5, Washington
PINNELL, EARL E., 760 Fidelity Building, Dayton 2, Ohio
PITOCK, MORRIS P., 1275 Post Road, Fairfield, Connecticut
PLATZ, CHARLES P., 451 Divine Avenue, Casper, Wyoming
POLLARD, WILLIAM E., 36 Rollingmead, Princeton, New Jersey
POOLE, CHARLES S., 1212 Fifth Avenue, New York 29, New York
PRATHER, JOHN W., 155 Washington Avenue, Dumont, New Jersey
PROUDFIT, CHARLES H., 515 I. O. O. F. Building, South Bend, Indiana
RANNELS, HERMAN W., 37 West Orange Street, Lancaster, Pennsylvania
RAPP, WILLIAM E., University of Nebraska, School of Medicine, Omaha, Nebraska
RAVENSCROFT, JAMES W., 233 A Street, San Diego 1, California
RECORDS, JOHN W., 301 Northwest Twelfth Street, Oklahoma City, Oklahoma
REINISCH, MAX, 310 Maple Street, Holyoke, Massachusetts
RENNING, ELISE L., 50 East Sixty-Fourth Street, New York, New York
RICE, HAROLD B., 314 Professional Building, 10 Peterboro Street, Detroit 1, Michigan
RICHARDSON, EDWARD H. (JR.), Nine East Chase Street, Baltimore 10, Maryland
RICHWINE, BARTON W., 900 Seventeenth Street, N. W., District of Columbia
RITT, ARNOLD E. F., 100 East Franklin Avenue, Minneapolis, Minnesota
ROBERTSON, DOUGLAS H., 22 Sagamore Road, Bronxville 8, New York
ROBINS, SPOTSWOOD, 810 West Franklin Street, Richmond 20, Virginia
ROGERS, GEORGE E. B., University of Minnesota Hospital, Minneapolis 14, Minnnesota
ROMBERGER, FLOYD T. (JR.), 3440 North Meridian Street, Indianapolis 8, Indiana
ROONEY, JOSEPH F., 40 East Sixty-Second Street, New York, New York
RUST, JESSE A. (JR.), 3115 University Avenue, San Diego 4, California
SAVAGE, MILLARD B., 402 Medical Arts Building, Norfolk, Virginia
SCALES, KENNETH J., 508 Medical Arts Building, Portland, Oregon
SCHADE, FRANK F., 1800 West Sixth Street, Los Angeles 5, California
SCHIRMER, ELIZABETH H., 812 S. W. Washington, Portland, Oregon
SCHUMACHER, PAUL C., 401 Park Avenue, Hamilton, Ohio
SCHUMAN, WILLIAM, 1716 Eutaw Place, Baltimore 17, Maryland
SCHWARTZ, SAUL F., 208 East Wisconsin Avenue, Milwaukee, Wisconsin
SCOTT, ROGER B., Johns Hopkins Hospital, Baltimore 5, Maryland
SEIDMAN, THEODORE R., 1160 Fifth Avenue, New York 29, New York
SELLS, ROBERT L., 77 San Mateo Drive, San Mateo, California
SEWALL, WESTON, 466 Commonwealth Avenue, Boston, Massachusetts
SHARP, GEORGE T. (JR.), 1835 Eye Street, N. W., Washington, D. C.
SHELDON, DEAN, 514 Wayne Street, Sandusky, Ohio.
SHELTON, CARL F., 910 Broderick Tower, Detroit 26, Michigan
SHERWIN, ANDREW S., 131 Fulton Avenue, Hempstead, New York
SHIVELY, J. PAUL, 1283, Thirty-fourth Avenue, San Francisco 22, California
SHULL, JOHN C., 179 Allyn Street, Hartford 3, Connecticut
SHULMAN, LEON J., 9615 Brighton Way, Beverly Hills, California
SILBERNAGEL, WYNNE M., Nine Buttles Avenue, Columbus, Ohio
SIMMONS, WALTER H. (JR.), 421 Standard Life Building, Jackson 27, Mississippi.
SIMON, HERBERT J., 20 East Seventy-Sixth Street, New York 21, New York
SIMPSON, JOHN W., 552 Graham Road, Fort Sam Houston, Texas
SINYKIN, MELVIN B., 400 Medical Arts Building, Minneapolis 2, Minn.
SMITH, CHARLES J., 1791 Howard Street, Chicago 26, Illinois
SOGHOR, SAMUEL, 727 West Seventh Street, Los Angeles 14, California
SOLOMON, ARTHUR, 24 Madison Avenue, Endicott, New York
STANTON, EDWARD F., 950 Park Avenue, New York, 28, New York
STEIN, PHILIP J., 900 West Argyle Street, Chicago, Illinois
STODDARD, FREDERICK J., 425 East Wisconsin Avenue, Milwaukee, Wisconsin
STURLEY, RODNEY F., 1240 Lowry Medical Arts Building, St. Paul, Minnesota
TAFEEN, CARL H., 142 Joralemon Street, Brooklyn, New York
TARR, DANSON, 719 North Central Avenue, Glendale, California
THIERSTEIN, SAMUEL T., 800 South Thirteenth Street, Lincoln 8, Nebraska
THORNTON, WILLIAM N. (JR.), University of Virginia Hospital, Charlottesville, Virginia
TREADWELL, WILLARD V., 1001 North Broadway, Santa Ana, California
TREGENZA, WILLIAM K., 17357 Fendell Avenue, Detroit 27, Michigan
TURNER, THOMAS E., 718 East Jefferson Street, Syracuse, New York
TYSON, THOMAS D. (JR.), 649 North Main Street, High Point, North Carolina
VARINO, GEORGE A., 521 Jackson Street, Monroe, Louisiana
WALSH, JOHN W., 2023 R Street, N. W., Washington 9, D. C.
WARREN, JOSEPH E., 1102 Church Street, Lynchburg, Virginia
WATSON, HARWOOD, 935 Military Avenue, Dearborn, Michigan
WATTS, ALICE D., 324 East Wisconsin Avenue, Milwaukee 2, Wisconsin
WEINROD, NORMAN M., 175 Crary Avenue, Mt. Vernon, New York

WEST, OTUS T., Employees Hospital, Fairfield, Alabama
WILLIAMS, WALTER, 643 South Wilton Place, Los Angeles 5, California
WILSON, JAMES M., Number Two, Trumbo Street, Charleston 28, South Carolina
WILSON, ROBERT B., 102-110 Second Avenue, S. W., Rochester, Minnesota
WINTHER, NORA M. C., 515 Medical Arts Building, Minneapolis 2, Minnesota
WIRTHWEIN, CARLTON, 425 East Wisconsin Avenue, Milwaukee 2, Wisconsin
WOLFROM, CARLOS E., 1930 Chestnut Street, Philadelphia, Pennsylvania
WOOD, WILLIAM R., 714 Summit Avenue, Greensboro, North Carolina
WOODRUFF, JAMES D., Six East Eager Street, Baltimore 2, Maryland
WRIGHT, ARTHUR F., 131 Fulton Avenue, Hempstead, New York
YOUNG, RAYMOND L., Lovelace Clinic, Albuquerque, New Mexico
ZACHARIAS, LLOYD F., 2500 Melrose Avenue, Cincinnati 6, Ohio
ZAKRZEWSKI, MATTHEW J., 255 South Seventeenth Street, Philadelphia, Pennsylvania
ZARKIN, OSCAR, 255 South Seventeenth Street, Philadelphia, Pennsylvania
ZIPRICK, HAROLD F., 312 North Boyle Avenue, Los Angeles, California

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The American Board of Obstetrics and Gynecology in annual session at Pittsburgh, Pa., June 1 to 7, 1947, announces the election of the following officers:

Walter T. Dannreuther, M.D., President, New York City, N. Y.; Joseph L. Baer, M.D., Vice-President, Chicago, Ill.; Ludwig A. Emge, M.D., Vice-President, San Francisco, Calif.; Paul Titus, M.D., Secretary-Treasurer, 1015 Highland Building, Pittsburgh, Pa.; Norman F. Miller, M.D., Member of Executive Committee, Ann Arbor, Mich.

The other members of the Board are: Willard R. Cooke, M.D., Galveston, Texas; F. Bayard Carter, M.D., Durham, N. C.; Edward A. Schumann, M.D., Philadelphia, Pa.; and Robert L. Faulkner, M.D., Cleveland, Ohio.

Announcement

The American Board of Obstetrics and Gynecology in annual session at Pittsburgh, Pa., June 1-7, 1947, announced the following statement of policy:

It was never intended by this Board that certification should be required by any hospital as a prerequisite to appointment in various staff positions, even though certification or its full equivalent is considered a desirable requisite to appointment in key positions, as on the Senior or Chief Staff, especially of hospitals expecting to conduct approved services for training of residents.

This Board does not subscribe to any Hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training.

The Board also adopted certain changes in regulations as follows:

Candidates will be hereafter required to present not merely a fundamental knowledge of both branches of the specialty, but evidence of actual adequate training in obstetrics and gynecology.

Credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months regardless of the duration of the course.

PAUL TITUS, M.D., Secretary.